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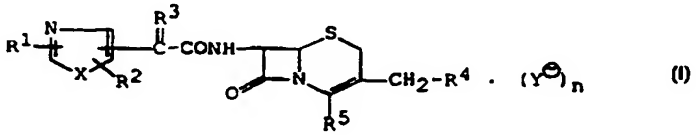
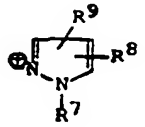


(I)

(a)



(b)

(57) Abstract

The present invention relates to a cephem compound of formula (I) wherein R^1 is amino, etc; R^2 is halogen, etc; R^3 is a group of formula (a) (wherein R^6 is hydrogen, etc); R^4 is a group of formula (b) (wherein R^7 is hydroxy(lower)alkyl, etc; R^8 is amino, etc; and R^9 is hydrogen, etc), etc; R^5 is $-COO^{\ominus}$, etc; X is -S- etc; $Y^{\ominus}$ is an anion, and n is 0 or 1, and a salt thereof, which is useful as a medicament; the processes for the preparation of said cephem compound or a salt thereof; a pharmaceutical composition comprising said cephem compound or a pharmaceutically acceptable salt thereof; etc.

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DESCRIPTION

3-Pyrazoliomethylcephem compounds as antimicrobial agents

TECHNICAL FIELD

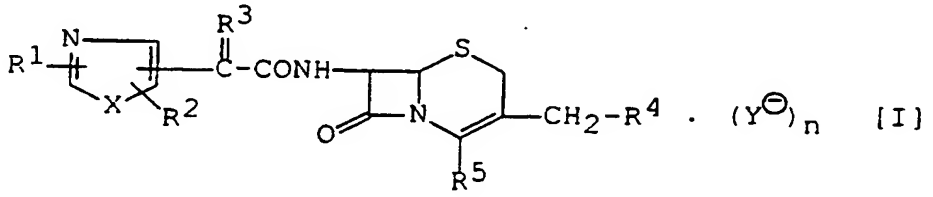
The present invention relates to a new cephem compound and a salt thereof which are useful as a medicament.

BACKGROUND ART

A cephem compound which is more effective against MRSA, etc is needed.

DISCLOSURE OF INVENTION

The object cephem compound of the present invention can be represented by the following formula [I] :

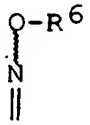


[I]

wherein R^1 is amino or a protected amino,

R^2 is halogen, lower alkyl, cyano or lower alkylthio,

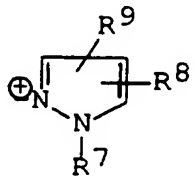
R^3 is a group of the formula :



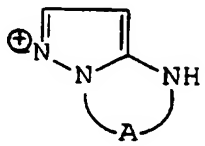
[wherein

R^6 is hydrogen, lower alkyl which may have one or more substituent(s), lower alkenyl which may have one or more substituent(s), lower alkynyl,

cyclo(lower)alkenyl, or acyl],
lower alkylidene or oxo,
R^4 is a group of the formula :



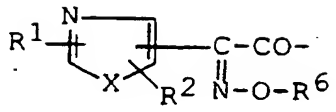
[wherein
R^7 is hydroxy(lower)alkyl or protected hydroxy(lower)alkyl,
R^8 is amino or a protected amino, and
R^9 is hydrogen or lower alkyl],
or a group of the formula :



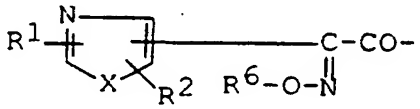
(wherein A is lower alkylene),
R^5 is $-COO^{\ominus}$, carboxy or a protected carboxy,
X is -S- or -O-,
$Y^{\ominus}$ is an anion, and
n is 0 or 1,
with proviso that
(i) when R^5 is $-COO^{\ominus}$, then n is 0, and
(ii) when R^5 is carboxy or a protected carboxy, then n is 1.

As to the object compound [I], the following points are to be noted.

That is, the object compound [I] includes Z isomer, E isomer and a mixture thereof. Z isomer means one geometrical isomer having the partial structure represented by the following formula :

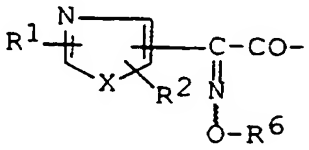


(wherein X, R^1, R^2 and R^6 are each as defined above), and E isomer means the other geometrical isomer having the partial structure represented by the following formula :



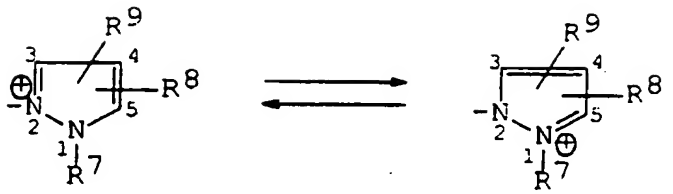
(wherein X, R^1, R^2 and R^6 are each as defined above), and all of such geometrical isomers and mixture thereof are included within the scope of this invention.

In the present specification and claim, the partial structure of these geometrical isomers and mixture thereof are represented for convenient sake by the following formula :



(wherein X, R^1, R^2 and R^6 are each as defined above).

Another point to be noted is that the pyrazolio moiety of the compound [I] can also exist in the tautomeric form, and such tautomeric equilibrium can be represented by the following scheme.

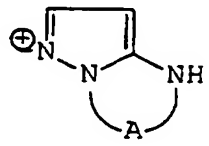


(A) (B)

(wherein R^7, R^8 and R^9 are each as defined above).

Both of the above tautomeric isomers are included within the scope of the present invention, and in the present specification and claim, however, the object compound [I] is represented for the convenient sake by one expression of the pyrazolio group of the formula (A).

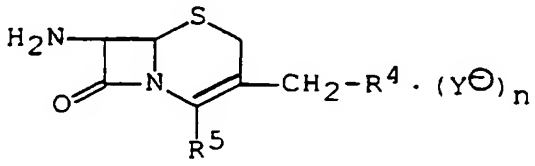
As for the group of the formula :



(wherein A is as defined above),
this group can also exist in the similar tautomeric form.

The cephem compound [I] of the present invention can be prepared according to the following reaction schemes.

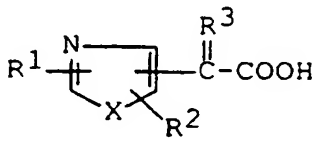
Process 1



[II]

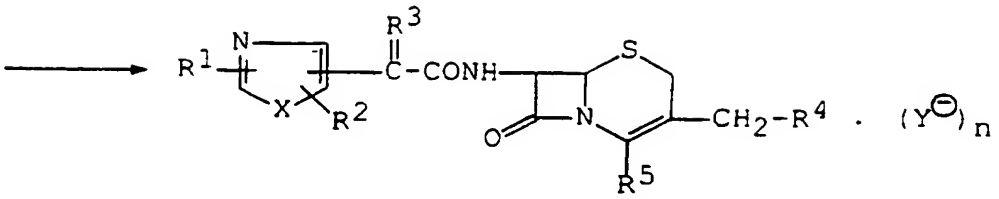
or its reactive derivative at the amino group, or a salt thereof

+



[III]

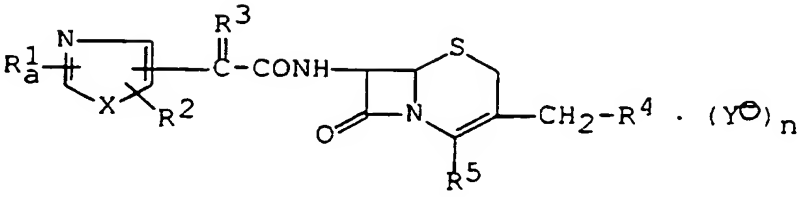
or its reactive derivative at the carboxy group, or a salt thereof



[I]

or a salt thereof

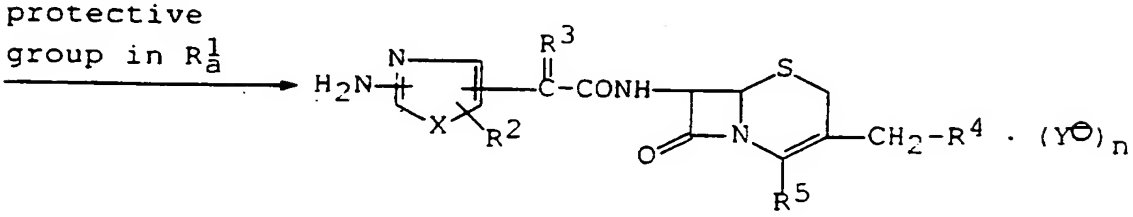
Process 2



[Ia]

or a salt thereof

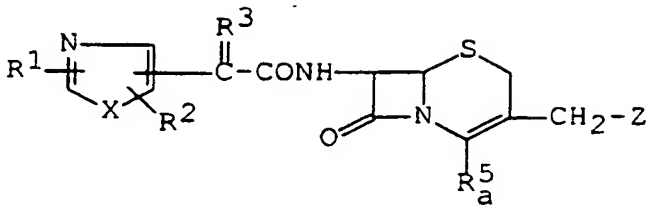
Elimination of the amino protective group in R_a^1



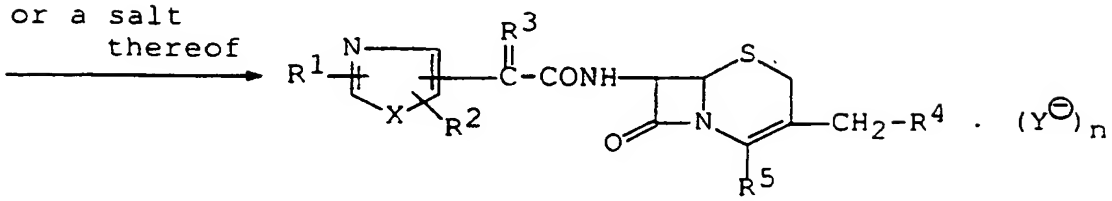
[Ib]

or a salt thereof

Process 3

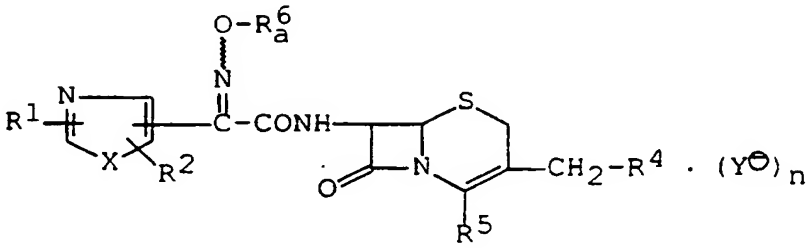


[IV]
or a salt thereof



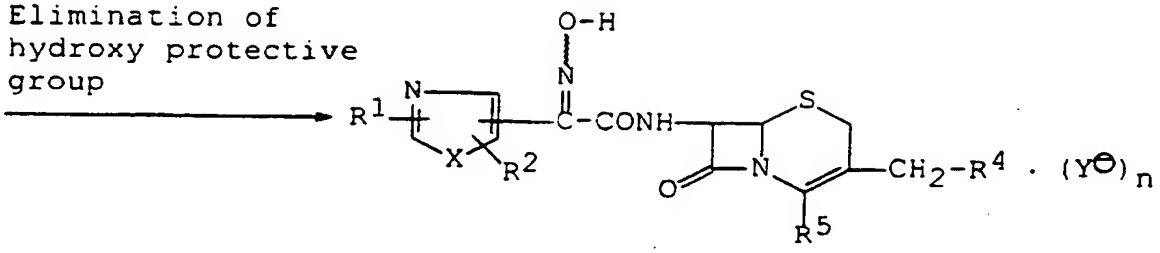
[I]
or a salt thereof

Process 4



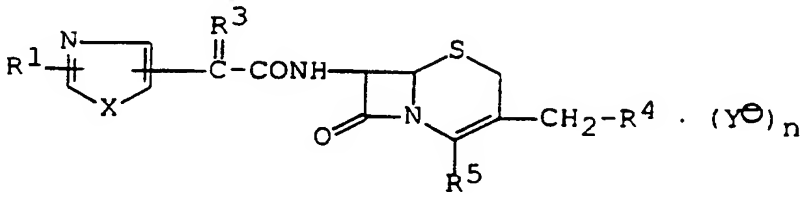
[Ic]
or a salt thereof

Elimination of hydroxy protective group



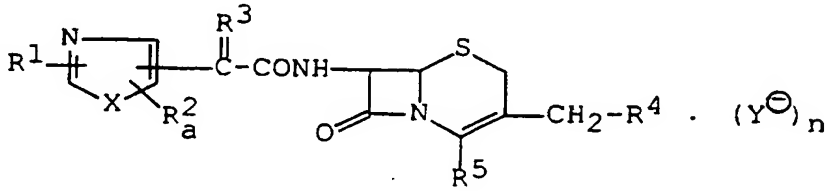
[Id]
or a salt thereof

Process 5



[VI]
or a salt thereof

Introduction reaction of halogen



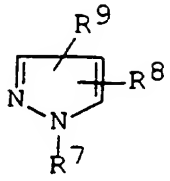
[Ie]
or a salt thereof

wherein R^1, R^2, R^3, R^4, R^5, X, $Y^{\ominus}$ and n are each as defined above,

R^1_a is a protected amino,

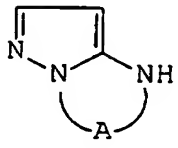
R^2_a is halogen,

R^4_a is a compound of the formula :



(wherein R^7, R^8 and R^9 are each as defined above)

or a compound of the formula :



(wherein A is as defined above),

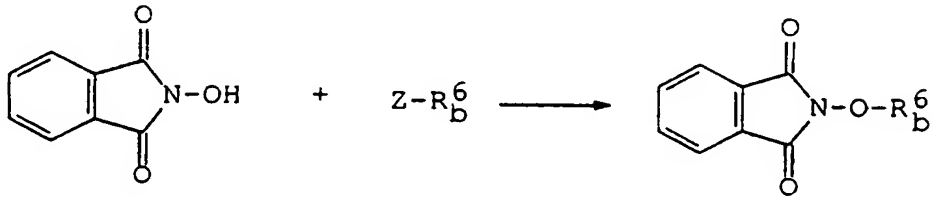
R_a^5 is carboxy or a protected carboxy,

R_a^6 is cyclo(lower)alkenyl or acyl,

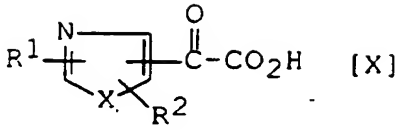
Z is a leaving group.

Some of the starting compound [III] can be prepared according to the following reaction schemes.

Process A



[VII] [VIII] [IX]

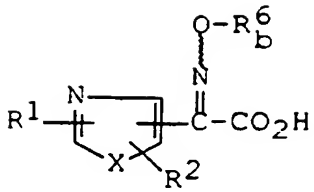


[X]

or a salt thereof

NH_2-NH_2 [XI]

or a salt thereof



[IIIa]

or a salt thereof

wherein R^1, R^2, X and Z are each as defined above, and R^6_b is lower alkyl which may have one or more substituent(s).

Suitable salts of the object compound [I] are pharmaceutically acceptable, conventional non-toxic mono or di salts and include a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N-dibenzylethylenediamine salt, etc], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc], an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc], a salt with an amino acid [e.g. arginine salt, aspartic acid salt, glutamic acid salt, etc], and the like.

In the above and subsequent descriptions of this specification, suitable examples of the various definitions are explained in detail as follows :

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable protective group in "a protected amino" may include ar(lower)alkyl such as mono or di or triphenyl(lower)alkyl [e.g. benzyl, phenethyl, 1-phenylethyl, benzhydryl, trityl, etc], acyl as explained hereinbelow, and the like.

Suitable "acyl" may be aliphatic acyl, aromatic acyl, arylaliphatic acyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbonic acid, carbamic acid, sulfonic acid, and the like.

Suitable example of the acyl group thus explained may be lower alkanoyl [e.g. formyl, acetyl, propionyl, hexanoyl, pivaloyl, etc], mono(or di or tri)halo(lower)alkanoyl [e.g. chloroacetyl, trifluoroacetyl, etc], lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, etc], mono(or di or tri)halo(lower)alkoxycarbonyl [e.g. chloromethoxycarbonyl, dichloroethoxycarbonyl, trichloroethoxycarbonyl, etc], aroyl [e.g. benzoyl, toluoyl, xyloyl, naphthoyl, etc], ar(lower)alkanoyl such as phenyl(lower)alkanoyl [e.g. phenylacetyl, phenylpropionyl, etc], aryloxycarbonyl [e.g. phenoxycarbonyl, naphthyloxycarbonyl, etc], aryloxy(lower)alkanoyl such as phenoxy(lower)alkanoyl [e.g. phenoxyacetyl, phenoxypropionyl, etc], arylglyoxyloyl [e.g. phenylglyoxyloyl, naphthylglyoxyloyl, etc], ar(lower)alkoxycarbonyl which may have suitable substituent(s) such as phenyl(lower)alkoxycarbonyl which may have nitro or lower alkoxy [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, etc], thienylacetyl, imidazolylacetyl, furylacetyl, tetrazolylacetyl, triazolylacetyl, thiadiazolylacetyl, thienylpropionyl, thiadiazolylpropionyl, lower alkylsulfonyl [e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, pentylsulfonyl, butylsulfonyl, etc], arylsulfonyl [e.g. phenylsulfonyl, tolylsulfonyl,

xylylsulfonyl, naphthylsulfonyl, etc], ar(lower)alkylsulfonyl such as phenyl(lower)alkylsulfonyl [e.g. benzylsulfonyl, phenethylsulfonyl, benzhydrylsulfonyl, etc], and the like.

Preferable example of "a protected amino" thus defined may be ar(lower)alkylamino, lower alkanoylamino and lower alkoxycarbonylamino, more preferable one may be triphenyl-(C_1-C_4)alkylamino, C_1-C_4 alkanoylamino and (C_1-C_4)-alkoxycarbonylamino, and the most preferable one may be tritylamino, formamido, acetamido and t-butoxycarbonylamino.

Suitable "lower alkyl" may be straight or branched ones such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, 2-ethylpropyl, hexyl or the like, in which the preferred "lower alkyl" may be (C_1-C_4)alkyl.

Suitable "lower alkenyl" may be straight or branched ones such as vinyl, allyl, 2-butenyl, 2-methyl-3-butenyl, 3-pentenyl, 1-hexenyl, or the like, in which the preferred one may be (C_2-C_4)alkenyl.

Suitable "lower alkynyl" may be straight or branched ones such as ethynyl, 2-propynyl, 3-butynyl, 2-methyl-3-butynyl, 2-pentynyl, 5-hexynyl, or the like, in which the preferred one may be (C_2-C_4)alkynyl.

Suitable "halogen" may be fluoro, chloro, bromo, or iodo.

Suitable examples of "substituent(s)" in "lower alkyl which may have one or more substituent(s)" may include 1 to 3 halogen; cyano; aryl [e.g. phenyl, naphthyl, anthryl, etc]; lower alkylthio ; carboxy; protected carboxy; hydroxy(lower)alkyl; protected hydroxy(lower)alkyl; heterocyclic group which may have one or more (preferably 1 to 3) substituent(s) such as lower alkyl, ar(lower)alkyl or the like; heterocyclicthio; and the like.

Suitable "lower alkylthio" may include methylthio, ethylthio, propylthio, butylthio, t-butylthio, pentylthio, hexylthio, and the like, in which the preferred one may be (C_1-C_4)alkylthio.

Suitable "protected carboxy" may be (1) an esterified carboxy, in which concrete examples of esterified carboxy may be the ones such as lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, 1-cyclopropylethoxycarbonyl, etc) which may have suitable substituent(s), for example, lower alkanoyloxy(lower)alkoxycarbonyl [e.g. acetoxymethoxycarbonyl, propionyloxymethoxycarbonyl, butyryloxymethoxycarbonyl, valeryloxymethoxycarbonyl, pivaloyloxymethoxycarbonyl, 1-acetoxyethoxycarbonyl, 1-propionyloxyethoxycarbonyl, pivaloyloxymethoxycarbonyl, 2-propionyloxyethoxycarbonyl, hexanoyloxymethoxycarbonyl, etc]; lower alkanesulfonyl(lower)alkoxycarbonyl [e.g. 2-mesylethoxycarbonyl, etc]; mono(or di or tri)halo(lower)alkoxycarbonyl [e.g. 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc]; lower alkenyloxycarbonyl [e.g. vinyloxycarbonyl, allyloxycarbonyl, etc]; lower alkynyloxycarbonyl [e.g. ethynyloxycarbonyl, propynyloxycarbonyl, etc]; ar(lower)alkoxycarbonyl [preferably mono-(or di- or tri-)phenyl(lower)alkoxycarbonyl] which may have suitable substituent(s) [e.g. benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, phenethyloxycarbonyl, trityloxycarbonyl, benzhydryloxycarbonyl, bis(methoxyphenyl)methoxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-hydroxy-3,5-di-t-butylbenzyloxycarbonyl, etc]; aryloxycarbonyl which may have suitable substituent(s) [e.g. phenoxycarbonyl, 4-chlorophenoxycarbonyl, tolyloxycarbonyl, 4-t-butylphenoxycarbonyl, xylyloxycarbonyl, mesityloxycarbonyl, cumenyloxycarbonyl, etc]; or the like; (2) amidated carboxy, in which concrete examples of amidated carboxy may be carbamoyl;

N-(lower)alkylcarbamoyl (e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N-isopropylcarbamoyl, N-butylcarbamoyl, N-pentylcarbamoyl, N-hexylcarbamoyl, etc);

N-(higher)alkylcarbamoyl (e.g. N-heptylcarbamoyl, N-(2-methylheptyl)carbamoyl, N-nonylcarbamoyl, N-decanylcarbamoyl, N-tricyclo[3.3.1.1^{3,7}]decanylcarbamoyl, N-undecanylcarbamoyl, N-(bicyclo[4.3.2]undecanyl)carbamoyl, N-dodecanylcarbamoyl, N-tridecanylcarbamoyl, N-tetradecanylcarbamoyl, N-pentadecanylcarbamoyl, N-hexadecanylcarbamoyl, N-heptadecanylcarbamoyl, N-octadecanylcarbamoyl, N-nonadecanylcarbamoyl, N-icosanylcarbamoyl, etc);

N,N-di(lower)alkylcarbamoyl [e.g. N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, N,N-dipropylcarbamoyl, N,N-di(t-butyl)carbamoyl, N-pentyl-N-hexylcarbamoyl, etc]; and the like,

in which the preferred one may be lower alkoxycarbonyl and carbamoyl, and the more preferred one may be (C_1-C_4)-alkoxycarbonyl and carbamoyl.

Suitable "hydroxy(lower)alkyl" may include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 3-hydroxypropyl, 1-(hydroxymethyl)ethyl, 1-hydroxybutyl, 1-hydroxymethyl-1-methylethyl, 3-hydroxypentyl, 3-hydroxy-2-ethylpropyl, 6-hydroxyhexyl and the like, in which the preferred one may be hydroxy(C_1-C_4)alkyl.

Suitable "protected hydroxy(lower)alkyl" may include acyloxy(lower)alkyl and the like, in which suitable "acyl" moiety can be referred to the ones as exemplified for "a protected amino" before and suitable examples of said "acyloxy(lower)alkyl may be lower alkanoyloxy(lower)alkyl [e.g. formyloxymethyl, 1-formyloxyethyl, 2-formyloxyethyl, 2-acetoxyethyl, 3-acetoxypropyl, 1-(propionyloxymethyl)ethyl, 1-butyryloxybutyl, 1-hexanoyloxybutyl, 1-pivaloyloxymethyl-1-methylethyl, 3-formyloxypentyl, 3-formyloxy-2-ethylpropyl, 6-acetoxyhexyl, etc], carbamoyloxy(lower)alkyl [e.g.

carbamoyloxymethyl, 1-carbamoyloxyethyl, 2-carbamoyloxyethyl, 3-carbamoyloxypropyl, 1-(carbamoyloxymethyl)ethyl, 1-carbamoyloxybutyl, 1-carbamoyloxymethyl-1-methylethyl, 3-carbamoyloxypentyl, 3-carbamoyloxy-2-ethylpropyl, 6-carbamoyloxyhexyl, etc] or the like;
in which the preferred one may be (C_1-C_4)alkanoyloxy-(C_1-C_4)alkyl or carbamoyloxy(C_1-C_4)alkyl and the most preferred one may be 2-formyloxyethyl, 2-acetoxyethyl or 2-carbamoyloxyethyl.

Suitable "heterocyclic group" and "heterocyclic" moiety in the term of "heterocyclicthio" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group such as

unsaturated 3 to 8-membered (more preferably 5 to 7-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, azepinyl (e.g. 1H-azepinyl, etc), pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc), tetrazolyl (e.g 1H-tetrazolyl, 2H-tetrazolyl, etc), etc;

saturated 3 to 8-membered (more preferably 5 to 7-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, perhydroazepinyl (e.g. perhydro-1H-azepinyl, etc), pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, quinoxalinyl, imidazopyridyl [e.g. imidazo[4,5-c]pyridyl, etc], tetrahydroimidazopyridyl [e.g. 4,5,6,7-tetrahydro[4,5-c]pyridyl, etc], etc;

saturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, 7-azabicyclo[2.2.1]heptyl,

3-azabicyclo[3.2.2]nonanyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc), etc;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc), dihydrothiazinyl, etc;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc;

saturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), and

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom

and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc; or the like.

Suitable examples of "substituent(s)" in the term of "heterocyclic group which may have one or more substituent(s)" may include 1 to 3 lower alkyl and ar(lower)alkyl, in which the preferred one may be (C_1-C_4)alkyl and triphenyl(C_1-C_4)alkyl.

Suitable "lower alkylidene" may include methylene, ethylidene, propylidene, 1-methylethylidene, butylidene, pentylidene, hexylidene, and the like, in which the preferred one may be (C_1-C_4)alkylidene.

Suitable "cyclo(lower)alkenyl" may be cyclo(C_3-C_8)-alkenyl such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl or the like, in which the preferred one may be cyclo(C_5-C_7)alkenyl such as cyclopentenyl, cyclohexenyl or cycloheptenyl.

Suitable examples of "substituent(s)" in lower alkenyl which may have one or more substituent(s)" may include 1 to 3 carboxy, protected carboxy, and the like, in which the preferred one may be carboxy and lower alkoxycarbonyl, the more preferred one may be carboxy and (C_1-C_4)alkoxycarbonyl.

Suitable "lower alkylene" may be straight or branched ones such as methylene, ethylene, trimethylene, methylethylene, tetramethylene, pentamethylene, hexamethylene or the like, in which the preferred one may be (C_1-C_4)-alkylene.

Suitable "an anion" may be formate, acetate,

trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, chloride, bromide, iodide, sulfate, phosphate, or the like.

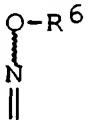
Suitable "a leaving group" may be halogen [e.g. chlorine, bromine, iodine, etc], acyloxy such as sulfonyloxy [e.g. benzenesulfonyloxy, tosyloxy, mesyloxy, etc], lower alkanoyloxy [e.g. acetyloxy, propionyloxy, etc], or the like.

One of the preferred embodiments of the present invention is the compound [I] wherein

R^1 is amino, lower alkanoylamino, lower alkoxycarbonylamino or triphenyl(lower)alkylamino,

R^2 is halogen, lower alkyl, cyano or lower alkylthio,

R^3 is a group of the formula :

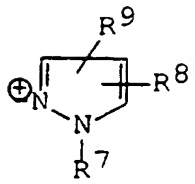


[wherein

R^6 is hydrogen; lower alkyl; halo(lower)alkyl; dihalo(lower)alkyl; cyano(lower)alkyl; triphenyl(lower)alkyl; lower alkylthio(lower)alkyl; carboxy(lower)alkyl; lower alkoxycarbonyl(lower)alkyl; carbamoyl(lower)alkyl; hydroxy(lower)alkyl; lower alkanoyloxy(lower)alkyl; pyrazolyl(lower)alkyl or tetrazolyl(lower)alkyl, each of which may have lower alkyl or triphenyl(lower)alkyl; triazolylthio(lower)alkyl; lower alkenyl; carboxy(lower)alkenyl; lower alkoxycarbonyl(lower)alkenyl; lower alkynyl; cyclo(lower)alkenyl; or lower alkanoyl],

lower alkylidene, or oxo,

R^4 is a group of the formula :



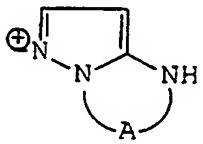
[wherein

R^7 is hydroxy(lower)alkyl, lower alkanoyloxy(lower)-alkyl, or carbamoyloxy(lower)alkyl,

R^8 is amino or lower alkanoylamino, and

R^9 is hydrogen], or

a group of the formula :



(wherein A is lower alkylene), and

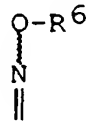
R^5, X, $Y^{\ominus}$ and n are each as defined above,

in which the more preferred one may be the compound [I] wherein

R^1 is amino,

R^2 is halogen, lower alkyl, cyano or lower alkylthio,

R^3 is a group of the formula :

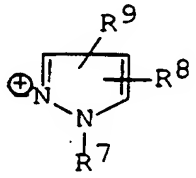


[wherein

R^6 is hydrogen; lower alkyl; halo(lower)alkyl; dihalo(lower)alkyl; cyano(lower)alkyl; triphenyl(lower)alkyl; lower alkylthio(lower)alkyl; carboxy(lower)alkyl; lower alkoxycarbonyl(lower)alkyl; carbamoyl(lower)alkyl; hydroxy(lower)alkyl; lower alkanoyloxy(lower)alkyl; pyrazolyl(lower)alkyl or

tetrazolyl(lower)alkyl, each of which may have lower alkyl or triphenyl(lower)alkyl; triazolylthio(lower)alkyl; lower alkenyl; carboxy(lower)alkenyl; lower alkoxycarbonyl(lower)alkenyl; lower alkynyl; cyclo(lower)alkenyl; or lower alkanoyl],

R^4 is a group of the formula :



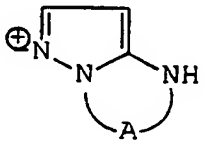
[wherein

R^7 is hydroxy(lower)alkyl, or

R^8 is amino, and

R^9 is hydrogen], or

a group of the formula :



(wherein A is lower alkylene),

R^5 is $-COO^{\ominus}$, and

X is -S-.

The processes for preparing the object compound of the present invention are explained in detail in the following.

Process 1

The object compound [I] or a salt thereof can be prepared by reacting a compound [II] or its reactive derivative at the amino group or a salt thereof with a compound [III] or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the amino group of the compound [II] may include Schiff's base type imino or its

tautomeric enamine type isomer formed by the reaction of the compound [II] with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound [II] with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound [II] with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound [II] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

Suitable reactive derivative at the carboxy group of the compound [III] may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc] or aromatic carboxylic acid [e.g. benzoic acid, etc]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g. cyanomethyl ester methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester,

8-quinolyl thioester, etc], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound [III] to be used.

Suitable salts of the compound [III] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylacetamide, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound [III] is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; phosphorus pentachloride; thionyl chloride; mesyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)-

isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, methanesulfonyl chloride, etc; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 2

The object compound [Ib] or a salt thereof can be prepared by subjecting a compound [Ia] or a salt thereof to elimination reaction of the amino protective group in R_a^1.

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc], an alkaline earth metal [e.g. magnesium, calcium, etc], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc].

The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reaction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc] or metallic compound [e.g. chromium chloride, chromium acetate, etc] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc], iron catalysts [e.g. reduced iron, Raney iron, etc], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such

as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc, or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 3

The object compound [I] or a salt thereof can be prepared by reacting a compound [IV] or a salt thereof with a compound [V] or a salt thereof.

Suitable salts of the compounds [IV] can be referred to the ones as exemplified for the compound [I].

Suitable salts of the compounds [V] may be an organic acid salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc], an inorganic acid salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc], or the like.

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, methanol, ethanol, diethyl ether, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound [V] is in liquid, it can also be used as a solvent. The reaction is preferably conducted in the presence of a base, for example, inorganic

base such as alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, organic base such as trialkylamine, and the like. The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating. The present reaction is preferably carried out in the presence of alkali metal halide [e.g. sodium iodide, potassium iodide, etc], alkali metal thiocyanate [e.g. sodium thiocyanate, potassium thiocyanate, etc] or the like.

Anion $Y^{\ominus}$ may be the one derived from a leaving group Z and may be the other one converted therefrom by a conventional method.

Process 4

The object compound [Id] or a salt thereof can be prepared by subjecting a compound [Ic] or a salt thereof to elimination reaction of the hydroxy protective group.

This reaction can be carried out in a similar manner to that of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent, reaction temperature, etc] of this reaction are to be referred to those as explained in Process 2.

Process 5

The object compound [Ie] or a salt thereof can be prepared by subjecting a compound [VI] or a salt thereof to introduction reaction of halogen.

This reaction can be carried out by reacting a compound [VI] or a salt thereof with an introduction agent of halogen such as N-halo-succinimide (e.g. N-bromosuccinimide, N-iodosuccinimide, etc), etc.

This reaction can be carried out in a solvent such as N,N-dimethylformamide, N,N-dimethylacetamide or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

The object compound [I] or a salt thereof can be prepared according to the methods other than Processes 1 to 5, and then can be carried out, for examples, as described in Examples.

The reactions in Process A for preparing the starting compound [III] or a salt thereof can be carried out according to the methods as described in Preparations or to the similar manners thereto.

In order to show the utility of the compound [I], the test data on MIC (minimal inhibitory concentration) of representative compound [I] of this invention is shown in the following.

Test Method :

In vitro antibacterial activity was determined by the two-fold agar-plate dilution method as described below.

One loopful of an overnight culture of each test strain in Trypticase-soy broth (10^6 viable cells per ml) was streaked on heart infusion agar (HI-agar) containing graded concentrations of representative test compound, and the minimal inhibitory concentration (MIC) was expressed in terms of μg/mℓ after incubation at 37°C for 20 hours.

Test Compound

(1) 7β-[(Z)-2-Cyanomethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate
(the compound of Example 8)

Test Result

MIC (μg/mℓ)

Test Bacteria	Test Compound (1)
S. aureus 3004	6.25

For therapeutic administration, the object compound [I] and a pharmaceutically acceptable salt thereof of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound [I] may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compound [I] to be applied, etc. In general, amounts between 1 mg and about 4,000 mg or even more per day may be administered to a patient. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg, 2000 mg of the object compound [I] of the present invention may be used in treating diseases infected by pathogenic microorganisms.

The following Preparations and Examples are given for the purpose of illustrating some preferred embodiments of the

present invention in more detail.

Preparation 1

A solution of bromoacetonitrile (8.82 g) in 67 ml of N,N-dimethylformamide was treated portionwise with N-hydroxyphthalimide (10.0 g) and powdered potassium carbonate (16.9 g) at 0°C. The mixture was allowed to stir at room temperature. The reaction mixture was poured into 670 ml of water to afford 8.03 g of N-(cyanomethoxy)phthalimide as precipitates.

IR (KBr) : 1740 cm^{-1}

NMR (DMSO-d_6, δ) : 7.92 (4H, s), 5.25 (2H, s)

Preparation 2

A solution of N-hydroxyphthalimide (3.38 g) and 1-bromo-2,2-difluoroethane (3.0 g) in 8 ml of N,N-dimethylformamide was treated with triethylamine (6.2 ml) at 0°C. The mixture was allowed to warm to 80°C. After 24 hours, additional 1-bromo-2,2-difluoroethane (1.5 g) in 4 ml of N,N-dimethylformamide was introduced. The reaction mixture was quenched by water and extracted with ethyl acetate. The combined extracts were washed with water, aqueous sodium hydrogen carbonate and brine, and were dried with magnesium sulfate. The solvent was removed under reduced pressure and the residue was washed with isopropyl ether to afford 3.50 g of N-(2,2-difluoroethoxy)phthalimide.

NMR (DMSO-d_6, δ) : 7.89 (4H, s), 6.34 (1H, tt, J=54Hz, 3.8Hz), 4.50 (1H, dd, J=14.2Hz, 3.8Hz), 4.43 (1H, dd, J=14.2Hz, 3.8Hz)

MS (APCI) m/z : 228 (M^++1)

Preparation 3

To a solution of N-(2-fluoroethoxy)phthalimide (9.3 g) in tetrahydrofuran (180 ml) was added dropwise hydrazine monohydrate (2.9 ml) under ice-cooling with stirring and the

mixture was stirred for 1.5 hours at 25 to 35°C. The insoluble material was filtered off, and the filtrate was adjusted to pH 7.0 with aqueous sodium hydrogen carbonate. To the neutral solution was added 2-(2-formylamino-5-chlorothiazol-4-yl)-2-oxoacetic acid (10.5 g), and the mixture was stirred at room temperature for 3 hours with keeping the pH value between 4.5-5.0 with saturated aqueous sodium hydrogen carbonate. The reaction mixture was poured into ethyl acetate (300 ml), and adjusted to pH 3.0 with 1N-hydrochloric acid. The separated organic phase was washed with water (200 ml) and dried with magnesium sulfate and evaporated in vacuo to give (Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-(2-fluoroethoxyimino)acetic acid (9.6 g).

NMR (DMSO-d_6, δ) : 4.25-4.35 (1H, m), 4.45-4.55 (1H, m), 4.50-4.60 (1H, m), 4.75-4.85 (1H, m), 8.55 (1H, s), 12.89 (1H, br s)

Preparation 4

A solution of N-(2,2-difluoroethoxy)phthalimide (1.94 g) in 39 ml of methanol and 14 ml of dichloromethane was treated with hydrazine monohydrate (0.64 g) at 0°C. The insoluble material was filtered off and 2-oxo-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid (2.0 g) was added to the filtrate at room temperature. After 3 hours, the insoluble material was filtered off and the solvent was removed under reduced pressure. Ethyl acetate was added and the insoluble material was filtered off again, and the filtrate was removed under reduced pressure, and the residue was washed with isopropyl ether to afford 2.44 g of (Z)-2-(2,2-difluoroethoxyimino)-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid.

IR (KBr) : 3169, 1720, 1659, 1068, 1045 cm^{-1}

NMR (DMSO-d_6, δ) : 8.55 (1H, s), 7.84 (1H, s), 6.26 (1H, tt, J=54.6Hz, 3.7Hz), 4.45 (1H, dd, J=14.5Hz,

3.7Hz), 4.37 (1H, dd, J=14.5Hz, 3.7Hz)

Preparation 5

(Z)-2-Cyanomethoxyimino-2-(5-chloro-2-formylaminothiazol-4-yl)acetic acid (12.61 g) was obtained according to a similar manner to that of Preparation 4.

NMR (DMSO-d_6, δ) : 12.93 (1H, s), 8.57 (1H, s), 5.16 (2H, s)

Example 1

A mixture of N,N-dimethylformamide (0.67 ml) and phosphorus oxychloride (0.8 ml) in tetrahydrofuran (20 ml) was stirring for 30 minutes at 5°C, (Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-allyloxyiminoacetic acid (2.09 g) was added thereto with stirring and ice-cooling, and the mixture was stirred for 30 minutes at 5°C to produce an activated acid solution. On the other hand, 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (2.3 g) was dissolved in a solution of mono-trimethylsilylacetamide (8 g) in N,N-dimethylformamide (23 ml) and tetrahydrofuran (23 ml). To the solution was at a time added the above obtained activated acid solution at 5°C and the mixture was stirred for 1.5 hours at 5°C. The resulting solution was poured into ethyl acetate (1 ℓ). The resulting powder was collected by filtration, and dried in vacuo to give 7β-[(Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-allyloxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (4.4 g).

NMR (DMSO-d_6, δ) : 3.2-3.40 (2H, m), 3.50-3.65 (2H, m), 4.05-4.55 (2H, m), 4.50-4.65 (2H, m), 5.05-5.40 (2H+2H, m), 5.15 (1H, d, J=4.9Hz), 5.80-6.05 (1H+1H+1H, m), 7.96 (2H, br s), 8.07 (1H, d, J=3.2Hz), 8.53 (1H, s), 9.74 (1H, d, J=8.4Hz), 12.9 (1H, s)

Example 2

A mixture of N,N-dimethylformamide (2.8 ml) and phosphorus oxychloride (3.4 ml) in tetrahydrofuran (90 ml) was stirred for 30 minutes at 5°C. (Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(2-fluoroethoxyimino)acetic acid (9 g) was added thereto with stirring and ice-cooling, and the mixture was stirred for 30 minutes at 5°C to produce an activated acid solution. On the other hand, 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (12.7 g) was dissolved in a solution of mono-trimethylsilylacetamide (44.4 g) in N,N-dimethylformamide (120 ml) and tetrahydrofuran (120 ml). To the solution was at a time added the above obtained activated acid solution at 5°C, and the mixture was stirred for 1.5 hours at 5°C. The resulting solution was poured into ethyl acetate (3 ℓ). The precipitate was collected by filtration and dried under reduced pressure. The powder was dissolved in water (300 ml), adjusted to pH 4.0 with aqueous sodium hydrogen carbonate and then subjected to column chromatography on HP-20 (Trademark : Mitsubishi Kasei Corporation) (500 ml), and eluted with 20% 2-propanol and the eluate was lyophilized to give 7β-[(Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-(2-fluoroethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (5.8 g).

IR (KBr) : 1774, 1673, 1608, 1542, 1284, 1068 cm^{-1}

NMR (DMSO-d_6, δ) : 2.96 and 3.24 (2H, ABq, J=17.1Hz), 3.40-3.60 (2H, m), 4.05-4.40 (2H+1H), 4.40-4.50 (1H, m), 4.50-4.60 (1H, m), 4.70-4.80 (1H, m), 5.04 (1H, d, J=4.9Hz), 5.07 and 5.23 (2H, ABq, J=18.0Hz), 5.68 (1H, dd, J=4.9Hz, 8.4Hz), 5.84 (1H, d, J=3.1Hz), 7.39 (2H, br s), 8.09 (1H, d, J=3.1Hz), 8.54 (1H, s), 9.68 (1H, d, J=8.4Hz)

Example 3

To a solution of (Z)-2-(2,2-difluoroethoxyimino)-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid (1.67 g) in 16 ml of N,N-dimethylacetamide, powdered potassium carbonate (0.74 g) and methanesulfonyl chloride (1.22 g) were added stepwise at 0°C. On the other hand, a suspension of 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (2.0 g) in 20 ml of N,N-dimethylacetamide was treated portionwise with N-(trimethylsilyl)acetamide (4.19 g) at room temperature. Both reaction mixture were combined at 0°C and stirred for 3 hours. The reaction was quenched by dropping into 300 ml of ethyl acetate to get precipitates, which were purified by column chromatography on HP-20 resin to get 0.71 g of 7β-[(Z)-2-(2,2-difluoroethoxyimino)-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 1772, 1676, 1650, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 9.71 (1H, d, J=8.4Hz), 8.53 (1H, s), 8.11 (1H, d, J=2.9Hz), 7.32 (2H, br s), 6.24 (1H, br t, J=54.6Hz), 5.82 (1H, d, J=2.9Hz), 5.65 (1H, dd, J=8.4Hz, 4.7Hz), 5.22, 5.06 (2H, ABq, J=14.9Hz), 5.03 (1H, d, J=4.7Hz), 4.2-4.6 (2H, m), 4.37 (2H, br t, J=14.6Hz), 3.5-3.7 (2H, m), 3.21, 2.94 (2H, ABq, J=16.9Hz)

MS (FAB) m/z : 635.1 (M^+), 637.1 (M^++2)

Example 4

7β-[(Z)-2-Cyanomethoxyimino-2-(5-chloro-2-formylamino-thiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (3.24 g) was obtained according to a similar manner to that of Example 3.

MS (FAB) m/z : 610.3 (M^+)

Example 5

To a suspension of 7β-[(Z)-2-(2-formylamino-5-

chlorothiazol-4-yl)-2-allyloxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (3.74 g) in methanol (37 ml) was added concentrated hydrochloric acid (2.9 ml) under stirring at 25°C to 30°C. The stirring was continued for 3 hours at 20°C to 30°C. The reaction mixture was poured into a cooled water (100 ml) and adjusted to pH 4.0 with saturated aqueous sodium hydrogen carbonate. To the resulting solution was evaporated in vacuo. The residue was subjected to column chromatography on HP-20 (200 ml), and eluted with 15% 2-propanol and the eluate was lyophilized to give 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-allyloxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (520 mg).

IR (KBr) : 1776, 1666, 1585, 1539, 1388, 1352, 1016 cm^{-1}

NMR (DMSO-d_6, δ) : 2.91 and 3.17 (2H, ABq, J=17Hz), 3.40-3.65 (2H, m), 4.20-4.60 (2H, m), 4.50-4.60 (2H, m), 4.99 (1H, d, J=5Hz), 5.05-5.50 (2H+2H, m), 5.61 (1H, dd, J=5Hz, 8Hz), 5.81 (1H, d, J=3Hz), 5.85-6.05 (1H, m), 7.27 (2H, br s), 7.41 (2H, br s), 8.10 (1H, d, J=3Hz), 9.54 (1H, d, J=8Hz)

Example 6

7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-(2-fluoroethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (2.75 g) was obtained according to a similar manner to that of Example 5.

IR (KBr) : 1772, 1612, 1538, 1392, 1355, 1064 cm^{-1}

NMR (DMSO-d_6, δ) : 2.94 and 3.21 (2H, ABq, J=17.2Hz), 3.40-3.65 (2H, m), 4.15-4.25 (1H, m), 4.25-4.50 (1H+1H, m), 4.55-4.65 (1H, m), 4.70-4.85 (1H, m), 5.01 (1H, d, J=4.8Hz), 5.04 (2H, ABq, J=18.2Hz), 5.62 (1H, dd, J=4.8Hz, 7.9Hz), 5.82 (1H, d, J=2.9Hz), 7.34 (2H, br s), 7.39 (2H, br s), 8.09 (1H, d, J=2.9Hz), 9.54 (1H, d, J=7.9Hz)

Example 7

A solution of 7β-[(Z)-2-(2,2-difluoroethoxyimino)-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.71 g) in 3.6 ml of methanol was treated with hydrochloric acid (0.47 ml), and stirred for 4 hours at room temperature. The reaction mixture was dropped into 300 ml of ethyl acetate to get precipitates, which were purified by column chromatography on HP-20 resin to get 0.40 g of 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(2,2-difluoroethoxyimino)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 1770, 1649, 1616 cm^{-1}

NMR (DMSO-d_6, δ) : 9.60 (1H, d, J=8.4Hz), 8.11 (1H, d, J=3.1Hz), 7.44 (2H, br s), 7.30 (2H, br s), 6.20 (1H, tt, J=54.9Hz, 3.7Hz), 5.82 (1H, d, J=3.1Hz), 5.61 (1H, dd, J=8.4Hz, 4.9Hz), 5.22, 5.05 (2H, ABq, J=15.1Hz), 5.00 (1H, d, J=4.9Hz), 4.2-4.6 (2H, m), 4.31 (2H, dt, J=3.7Hz, 14.1Hz), 3.5-3.7 (2H, m), 3.20, 2.93 (2H, ABq, J=17.6Hz)

MS (FAB) m/z : 606.9 (M^+), 609.1 (M^++2)

Example 8

7β-[(Z)-2-Cyanomethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]-methyl-3-cephem-4-carboxylate (92 mg) was obtained according to a similar manner to that of Example 7.

IR (KBr) : 1770, 1666, 1614 cm^{-1}

NMR (DMSO-d_6, δ) : 9.72 (1H, d, J=8.4Hz), 8.11 (1H, d, J=3.2Hz), 7.49 (2H, br s), 7.28 (2H, br s), 5.81 (1H, d, J=3.2Hz), 5.59 (1H, dd, J=8.4Hz, 4.9Hz), 5.19, 5.07 (2H, ABq, J=15Hz), 5.01 (1H, d, J=4.9Hz), 5.00 (2H, s), 4.2-4.6 (2H, m), 3.2-3.8 (2H, m), 2.88, 3.21 (2H, ABq, J=17.1Hz)

MS (FAB) m/z : 582.0 (M^+), 584.1 (M^++2)

Preparation 6

A solution of ethyl 2-hydroxyimino-3-oxopentanoate (20 g) in 140 ml of ethyl acetate was treated with diethyl sulfate (19.59 g) and powdered potassium carbonate (18.36 g). The reaction mixture was quenched by water and extracted with ethyl acetate. The combined extracts were washed with water and brine, and were dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 19:1) to afford 11.11 g of ethyl 2-ethoxyimino-3-oxopentanoate.

IR (Neat) : 1747, 1695 cm^{-1}

NMR (DMSO-d_6, δ) : 1.00 (3H, t, J=7.3Hz), 1.23 (3H, t, J=7.1Hz), 1.27 (3H, t, J=7.1Hz), 2.81 (2H, q, J=7.3Hz), 4.27 (2H, q, J=7.1Hz), 4.32 (2H, q, J=7.1Hz)

Preparation 7

A solution of ethyl 2-ethoxyimino-3-oxopentanoate (11.11 g) in 11 ml of acetic acid was treated dropwise with sulfuryl chloride (5.06 ml). The mixture was stirred for 3 hours at 50°C and quenched by ice-water. The mixture was extracted with ethyl acetate, and the combined extracts were washed with brine and dried with magnesium sulfate. The solvent was removed under reduced pressure to afford 14.15 g of ethyl 4-chloro-2-ethoxyimino-3-oxopentanoate.

IR (Neat) : 1747, 1705 cm^{-1}

NMR (DMSO-d_6, δ) : 1.25 (3H, t, J=7.1Hz), 1.29 (3H, t, J=7.0Hz), 1.59 (3H, d, J=6.7Hz), 4.31 (2H, q, J=7.1Hz), 4.38 (1H, q, J=7.0Hz), 5.33 (1H, q, J=6.7Hz)

Preparation 8

A solution of ethyl 4-chloro-2-ethoxyimino-3-

oxopentanoate (14.15 g) in 44 ml of water and 44 ml of ethanol was treated portionwise with thiourea (6.86 g) and sodium acetate (7.39 g) at room temperature. The mixture was allowed to stir at 40°C. The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the precipitates were filtered and washed with water and dried under reduced pressure to afford 10.17 g of ethyl (Z)-2-ethoxyimino-2-(2-amino-5-methylthiazol-4-yl)acetate.

IR (KBr) : 3138, 1724, 1630, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 1.21 (3H, t, J=7.0Hz), 1.24 (3H, t, J=7.1Hz), 2.36 (3H, s), 4.12 (2H, q, J=7.0Hz), 4.23 (2H, q, J=7.1Hz), 6.95 (2H, s)

Preparation 9

A solution of ethyl (Z)-2-ethoxyimino-2-(2-amino-5-methylthiazol-4-yl)acetate (10.0 g) in 50 ml of tetrahydrofuran was treated with 19.4 ml of 4N sodium hydroxide solution. The reaction mixture was allowed to 50°C, and then diluted with water and washed with ethyl acetate. Aqueous phase was allowed to pH 2.5 to afford 7.60 g of (Z)-2-ethoxyimino-2-(2-amino-5-methylthiazol-4-yl)acetic acid as precipitates.

IR (KBr) : 1628 cm^{-1}

NMR (DMSO-d_6, δ) : 1.22 (3H, t, J=7.0Hz), 2.36 (3H, s), 4.10 (2H, q, J=7.0Hz), 6.94 (2H, s),

Preparation 10

A solution of ethyl (Z)-2-methoxyimino-2-(2-formylaminothiazol-4-yl)acetate (5.0 g) in 50 ml of methanol was treated with N-bromosuccinimide (3.81 g). The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were dried with sodium sulfate. The solvent was removed under reduced pressure to afford 6.8 g of ethyl (Z)-2-methoxyimino-2-(5-bromo-2-

formylaminothiazol-4-yl)acetate.

NMR (DMSO-d_6, δ) : 1.28 (3H, t, J=7.1Hz), 3.96 (3H, s), 4.31 (2H, q, J=7.1Hz), 8.55 (1H, s), 12.84 (1H, s)

MS (APCI) m/z : 336 (M^+)

Preparation 11

A solution of ethyl (Z)-2-methoxyimino-2-(5-bromo-2-formylaminothiazol-4-yl)acetate (6.8 g) in 68 ml of N,N-dimethylformamide was treated with copper(I) cyanide (2.17 g). The reaction mixture was allowed to 100°C. The reaction was quenched with ice-water, and extracted with ethyl acetate. The solvent was removed under reduced pressure to afford 1.60 g of ethyl (Z)-2-methoxyimino-2-(5-cyano-2-formylaminothiazol-4-yl)acetate.

IR (KBr) : 2222, 1743, 1691, 1531 cm^{-1}

NMR (DMSO-d_6, δ) : 1.30 (3H, t, J=6.7Hz), 4.04 (3H, s), 4.35 (2H, q, J=6.7Hz), 8.70 (1H, s), 13.36 (1H, s),

MS (APCI) m/z : 283 (M^++1)

Preparation 12

A solution of ethyl (Z)-2-methoxyimino-2-(5-cyano-2-formylaminothiazol-4-yl)acetate (0.8 g) in 3.2 ml of dioxane and 3.2 ml of water was treated with sodium hydroxide (0.57 g). After 3 hours, the reaction mixture was diluted with water and washed with ethyl acetate. Aqueous phase was allowed to pH 2 and extracted with ethyl acetate and tetrahydrofuran. The solvent was removed under reduced pressure to afford 0.59 g of (Z)-2-methoxyimino-2-(5-cyano-2-formylaminothiazol-4-yl)acetic acid.

IR (KBr) : 2218, 1741 cm^{-1}

MS (FAB) m/z : 255.0 (M^+)

Preparation 13

A solution of ethyl 2-(2-formylaminothiazol-4-yl)-2-oxoacetate (50 g) in 280 ml of N,N-dimethylformamide was

treated with a solution of trichloroisocyanuric acid (20.2 g) in 70 ml of N,N-dimethylformamide at 60°C. The reaction mixture was poured into 3.5 ℓ of ice-water to afford 54.15 g of ethyl 2-(5-chloro-2-formylaminothiazol-4-yl)-2-oxoacetate as precipitates.

IR (KBr) : 1749, 1676, 1543, 1086 cm^{-1}

NMR (DMSO-d_6, δ) : 1.32 (3H, t, J=7.1Hz), 4.38 (2H, q, J=7.1Hz), 8.60 (1H, s), 12.8 (1H, br s)

Preparation 14

Ethyl 2-(5-chloro-2-formylaminothiazol-4-yl)-2-oxoacetate (20 g) was added to 45 ml of 4N potassium hydroxide solution. The reaction mixture was diluted with water and washed with ethyl acetate. The aqueous phase was allowed to pH 2, and precipitates were filtered and washed with isopropyl ether to get 15.59 g of 2-(5-chloro-2-formylaminothiazol-4-yl)-2-oxoacetic acid.

NMR (DMSO-d_6, δ) : 8.59 (1H, s), 13.56 (1H, br s)

Preparation 15

A solution of (Z)-2-difluoromethoxyimino-2-(2-tritylaminothiazol-4-yl)acetic acid (20 g) in 300 ml of methanol was treated with N-chlorosuccinimide (6.13 g) and stirred at 70°C. After 7 hours, additional N-chlorosuccinimide (1.67 g) was introduced. The reaction mixture was diluted with water and allowed to pH 7, and washed with ethyl acetate. The aqueous phase was allowed to pH 2.6, and was extracted with ethyl acetate. The combined extracts were dried with sodium sulfate. The solvent was removed under reduced pressure to afford 8.88 g of (Z)-2-difluoromethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetic acid.

IR (KBr) : 3305, 3201, 1707, 1645 cm^{-1}

NMR (DMSO-d_6, δ) : 7.20 (1H, t, J=70.8Hz), 7.60 (2H, br s)

MS (APCI) m/z : 272 (M^++1)

Preparation 16

N-(Fluoromethoxy)phthalimide was prepared according to a similar manner to that of Preparation 1.

NMR (DMSO-d_6, δ) : 5.78 (2H, d, J=53.0Hz), 7.91 (4H, s)

MS (APCI) m/z : 195 (M^+)

Preparation 17

(Z)-2-Fluoromethoxyimino-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid was obtained according to a similar manner to that of Preparation 3.

IR (KBr) : 1739, 1720, 1685 cm^{-1}

NMR (DMSO-d_6, δ) : 5.82 (2H, d, J=55.1Hz), 8.57 (1H, s), 12.94 (1H, br s)

MS (APCI) m/z : 281.7 (M^+)

Preparation 18

A solution of ethyl 2-hydroxyimino-3-oxopentanoate (8.0 g) in 56 ml of ethyl acetate was treated with dimethyl sulfate (6.41 g) and powdered potassium carbonate (7.34 g). The reaction mixture was quenched by water and extracted with ethyl acetate. The combined extracts were washed with water and brine, and were dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 19:1) to afford 6.73 g of ethyl 2-methoxyimino-3-oxopentanoate.

IR (Neat) : 1747, 1697 cm^{-1}

NMR (DMSO-d_6, δ) : 1.00 (3H, t, J=7.3Hz), 1.24 (3H, t, J=7.1Hz), 2.81 (2H, q, J=7.3Hz), 4.06 (3H, s), 4.27 (2H, q, J=7.1Hz)

Preparation 19

Ethyl 4-chloro-2-methoxyimino-3-oxopentanoate was

obtained according to a similar manner to that of Preparation 7.

IR (Neat) : 1743, 1701, 1039 cm^{-1}

NMR (DMSO-d_6, δ) : 1.25 (3H, t, J=7.1Hz), 1.59 (3H, d, J=6.7Hz), 4.12 (3H, s), 4.31 (2H, q, J=7.1Hz), 5.31 (1H, q, J=6.7Hz)

MS (APCI) m/z : 222 (M^++1)

Preparation 20

Ethyl (Z)-2-methoxyimino-2-(2-amino-5-methylthiazol-4-yl)acetate was obtained according to a similar manner to that of Preparation 8.

NMR (DMSO-d_6, δ) : 1.24 (3H, t, J=7.1Hz), 2.36 (3H, s), 3.87 (3H, s), 4.23 (2H, q, J=7.1Hz) 6.94 (2H, br s),

MS (APCI) m/z : 244 (M^++1)

Preparation 21

(Z)-2-Methoxyimino-2-(2-amino-5-methylthiazol-4-yl)acetic acid was obtained according to a similar manner to that of Preparation 9.

NMR (DMSO-d_6, δ) : 2.36 (3H, s), 3.85 (3H, s), 6.96 (2H, br s)

MS (APCI) m/z : 216 (M^++1)

Preparation 22

N-(Carbamoylmethoxy)phthalimide was obtained according to a similar manner to that of Preparation 1.

NMR (DMSO-d_6, δ) : 4.60 (2H, s), 7.63 (2H, br s), 7.89 (4H, s)

Preparation 23

(Z)-2-Carbamoylmethoxyimino-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid was obtained according to a similar manner to that of Preparation 3.

NMR (DMSO-d_6, δ) : 4.55 (2H, s), 7.09 (1H, br s), 7.46 (1H, br s), 8.56 (1H, s), 12.92 (1H, s)

MS (APCI) m/z : 306.9 (M^+)

Preparation 24

(Z)-2-(1-tert-Butoxycarbonyl-1-methylethoxyimino)-2-(2-amino-5-chlorothiazol-4-yl)acetic acid was obtained according to a similar manner to that of Preparation 15.

IR (KBr) : 1732, 1720, 1645, 1146 cm^{-1}

NMR (DMSO-d_6, δ) : 1.39 (9H, s), 1.42 (6H, s), 7.43 (2H, br s)

MS (APCI) m/z : 364.2 (M^++1)

Preparation 25

To a solution of N-(cyanomethoxy)phthalimide (10.0 g) in tetrahydrofuran (100 ml) was added sodium azide (9.65 g) and aluminum chloride (7.26 g) at 0°C. The reaction mixture was refluxed with stirring. The reaction was quenched by 2N hydrochloric acid. The aqueous phase was extracted with ethyl acetate, and the combined extracts were washed with brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was washed with isopropyl ether to afford 6.33 g of N-(2H-tetrazol-5-ylmethoxy)phthalimide.

NMR (DMSO-d_6, δ) : 5.50 (2H, s), 7.8-8.0 (4H, m)

MS (APCI) m/z : 246 (M^++1)

Preparation 26

To a solution of N-(2H-tetrazol-5-ylmethoxy)phthalimide (2.32 g) in dimethylformamide (20 ml) was added trityl chloride (2.90 g) and triethylamine (1.6 ml) at 0°C. After 4 hours, the reaction was quenched by water and extracted with ethyl acetate. The combined extracts were washed with brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was washed with

hexane-ethyl acetate to afford 2.62 g of the mixture of N-(1-trityl-1H-tetrazol-5-ylmethoxy)phthalimide and N-(2-trityl-2H-tetrazol-5-ylmethoxy)phthalimide.

NMR (DMSO-d_6, δ) : 5.48 (2H, s), 6.9-7.0 (6H, m), 7.2-7.5 (9H, m), 7.8-7.9 (4H, m)

Preparation 27

A mixture of 2-[(Z)-(1-trityl-1H-tetrazol-5-ylmethoxyimino)]-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid and 2-[(Z)-(2-trityl-2H-tetrazol-5-ylmethoxyimino)]-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid were obtained according to a similar manner to that of Preparation 3.

IR (KBr) : 3427, 1732, 1691, 1547 cm^{-1}

NMR (DMSO-d_6, δ) : 5.49 (2H, s), 7.0-7.1 (6H, m), 7.2-7.4 (9H, m), 8.54 (1H, s), 12.88 (1H, s)

Preparation 28

A mixture of ethyl chlorofluoroacetate (100 g), phthaloyl chloride (102.5 ml) and chlorosulfonic acid (47.3 ml) was heated at total reflux in a still conncected to an ice-cooled receiver backed up by a dry ice cooled trap when the pot temperature reached 120°C, distillation was started and the volatile material was distilled from the reaction mixture until the pot temperature rose to 200°C. The condensates in the receiver and the dry ice cooled trap were combined. On the other hand, isopropylidene malonate (51.3 g) was dissolved in a solution of pyridine (69.7 ml) in dichloromethane (160 ml). To the solution was added dropwise above obtained combined solution at 5°C to 10°C and the mixture was stirred for 3 hours at the same temperature. The resulting solution was poured into a cooled 3N-hydrochloric acid (200 ml). The separated organic phase was washed with brine (200 ml), and dried with magnesium sulfate and evaporated in vacuo. The residue was added methanol (300 ml) at room temperature with stirring. The mixture was refluxed

for 8 hours. The reaction mixture was evaporated in vacuo. The residue was subjected to a column chromatography on silica gel (500 g) and eluted with a mixture of ethyl acetate and hexane (1:2). The fractions containing the objective compound were collected, evaporated to give methyl 4-chloro-4-fluoro-3-oxobutyrate (43.2 g).

NMR (DMSO-d_6, δ) : 3.72 (3H, s), 3.88 (2H, d, J=1.6Hz), 6.99 (1H, d, J=49Hz)

Preparation 29

To a solution of methyl 4-chloro-4-fluoro-3-oxobutyrate (31 g) and isopentylnitrite (25.8 ml) in dichloromethane (120 ml) was added dropwise acetyl chloride (13 ml) under ice-cooling with stirring and the mixture was stirred for 3 hours at 5°C to 10°C. The resulting solution was poured into water (300 ml) and adjusted to pH 3.0 with saturated aqueous sodium hydrogencarbonate. The separated organic phase was washed with water (300 ml) and dried with magnesium sulfate and evaporated in vacuo to give methyl 4-chloro-4-fluoro-2-hydroxyimino-3-oxobutyrate (44.5 g).

NMR (DMSO-d_6, δ) : 3.82 (3H, s), 7.39 (1H, d, J=49Hz), 14.14 (1H, s)

Preparation 30

To a solution of methyl 4-chloro-4-fluoro-2-hydroxyimino-3-oxobutyrate (7.8 g) in N,N-dimethylacetamide (80 ml) was added thiourea (15 g) under stirring at 30°C and then the stirring was continued for 12 hours at the same temperature. The resulting solution was poured into a mixture of ethyl acetate (300 ml) and water (400 ml), and adjusted to pH 3.0 with saturated aqueous sodium hydrogencarbonate. The separated organic phase was washed with water (400 ml) and brine (400 ml), and dried with magnesium sulfate and evaporated in vacuo to give methyl (Z)-2-(2-amino-5-fluorothiazol-4-yl)-2-hydroxyiminoacetate (2.17 g).

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 7.11 (2H, br s), 11.92 (1H, s)

Preparation 31

To a suspension of methyl (Z)-2-(2-amino-5-fluorothiazol-4-yl)-2-hydroxyiminoacetate (1 g) in dichloromethane (20 ml) was added dropwise borontrichloride 1M solution in dichloromethane (22.8 ml) under ice-cooling with stirring and the mixture was stirred for 3 hours at 5°C to 10°C. The resulting solution was poured into a mixture of tetrahydrofuran (30 ml) and brine (15 ml), and adjusted to pH 3.0 with saturated aqueous sodium hydrogencarbonate. The separated organic phase was dried with magnesium sulfate and evaporated in vacuo. The residue was subjected to a column chromatography on silica gel and eluted with a mixture of ethyl acetate and methanol (2:1). The fractions containing the object compound were combined and evaporated in vacuo to give (Z)-2-(2-amino-5-fluorothiazol-4-yl)-2-hydroxyimino-acetic acid (330.26 mg).

NMR (DMSO-d_6, δ) : 6.94 (2H, br s)

MS : 206 (M^+)

Preparation 32

A mixture of acetic anhydride (2.7 ml) and formic acid (2.2 ml) was stirred for 30 minutes at 30°C. (Z)-2-(2-Amino-5-fluorothiazol-4-yl)-2-hydroxyiminoacetic acid (1.2 g) was added thereto with stirring under ice-cooling, and the mixture was stirred for 3 hours at 25°C to 35°C. The reaction mixture was poured into an isopropyl ether (50 ml). The precipitate was collected by filtration, dried under reduced pressure to give (Z)-2-(2-formylamino-5-fluorothiazol-4-yl)-2-formyloxyiminoacetic acid.

NMR (DMSO-d_6, δ) : 8.23 (1H, s), 8.50 (1H, s)

Preparation 33

Methyl 4-chloro-4-fluoro-2-ethoxyimino-3-oxobutyrate was obtained according to a similar manner to that of Preparation 6.

NMR (DMSO-d_6, δ) : 1.37 (3H, t, J=7Hz), 3.85 (3H, s), 4.05 (2H, m), 7.38 (1H, d, J=49Hz)

Preparation 34

Methyl (Z)-2-(2-amino-5-fluorothiazol-4-yl)-2-ethoxyiminoacetate was obtained according to a similar manner to that of Preparation 8.

IR (KBr) : 1743, 1631, 1538, 1438, 1299, 1078 cm^{-1}

NMR (DMSO-d_6, δ) : 1.19 (3H, t, J=7Hz), 3.78 (3H, s), 4.13 (2H, q, J=7Hz), 7.20 (2H, br s)

Preparation 35

(Z)-2-(2-Amino-5-fluorothiazol-4-yl)-2-ethoxyiminoacetic acid was obtained according to a similar manner to that of Preparation 31.

IR (KBr) : 1637, 1604, 1533, 1407, 1359, 1216, 1041 cm^{-1}

NMR (DMSO-d_6, δ) : 1.76 (3H, t, J=7Hz), 3.60 (2H, q, J=7Hz)

Preparation 36

To a suspension of (Z)-2-(2-tritylaminothiazol-4-yl)-2-(2-fluoroethoxyimino)acetic acid in methanol (50 ml), was added N-bromosuccinimide (2.8 g) at room temperature with stirring and the mixture was stirred for 3 hours at 25°C to 35°C. The resulting solution was poured into a mixture of ethyl acetate (250 ml) and water (300 ml), and adjusted to pH 3.0 with aqueous sodium hydrogen carbonate. The separated organic phase was washed with water (200 ml) and dried with magnesium sulfate and evaporated in vacuo to give (Z)-2-(2-amino-5-bromothiazol-4-yl)-2-(2-fluoroethoxyimino)acetic acid (2.64 g).

NMR (DMSO-d_6, δ) : 4.10-4.15 (1H, m), 4.18-4.23 (1H, m),

4.55-4.60 (1H, m), 4.75-4.80 (1H, m), 7.45 (2H, br s)

Preparation 37

(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(2-acetoxyethoxyimino)acetic acid was obtained according to a similar manner to that of Preparation 3.

NMR (DMSO-d_6, δ) : 2.00 (3H, s), 4.05-4.30 (4H, m), 8.52 (1H, s)

Preparation 38

(Z)-2-(2-Formylaminothiazol-4-yl)-2-(methylthiomethoxyimino)acetic acid (10 g) was suspended into methanol (100 ml), N-bromosuccinimide (9.7 g) was added thereto at room temperature with stirring and the mixture was stirred for 3 hours at 20°C to 30°C. The resulting solution was poured into a mixture of ethyl acetate (300 ml) and water (300 ml), and adjusted to pH 3.0 with aqueous sodium hydrogencarbonate. The separated organic phase was washed with water (200 ml) and dried with magnesium sulfate and evaporated in vacuo. The residue was suspended into methanol (100 ml), thereto was added concentrated hydrochloric acid (17.2 ml) at room temperature. After the reaction mixture was stirred at room temperature for 4 hours, it was poured into a mixture of ethyl acetate (400 ml) and water (300 ml). The mixture was adjusted to pH 3.0 with aqueous sodium hydrogen carbonate. The separated organic phase was washed with water (300 ml) and dried with magnesium sulfate and evaporated in vacuo, to give (Z)-2-(2-amino-5-bromothiazol-4-yl)-2-(methylthiomethoxyimino)acetic acid (5.5 g).

IR (KBr) : 1704, 1639, 1538, 1376, 1297, 1180, 983 cm^{-1}

NMR (DMSO-d_6, δ) : 2.21 (3H, s), 5.34 (2H, s), 7.49 (2H, br s)

Preparation 39

To a solution of bromochloromethane (26.4 ml) and

N,N-dimethylformamide (160 ml) was added portionwise 4-mercapto-1H-1,2,3-triazole sodium salt(20 g) at -20°C, then it was stirred under ice-cooling for 20 minutes, at room temperature for one hour. The reaction mixture was poured into ethyl acetate (500 ml) and water (700 ml), it was adjusted to pH 7. The organic layer was separated, dried over magnesium sulfate, and evaporated. The residue was dissolved in N,N-dimethylformamide (250 ml) and pyridine (12.6 g), and triphenylmethylchloride (44.6 g) was added to the solution under ice-cooling. After the reaction mixture was stirred at room temperature for 2 hours, it was poured into ethyl acetate (750 ml) and water (900 ml), adjusted to pH 3.5. The organic layer was separated, dried over magnesium sulfate, and concentrated. The resulting precipitate was collected by filtration, and the precipitate was washed with diisopropyl ether. 5-Chloromethylthio-1-trityl-1H-1,2,3-triazole (38.2 g) was obtained.

NMR (DMSO-d_6, δ) : 5.25 (2H, s), 7.00-7.10 (6H, m), 7.35-7.43 (9H, m), 8.03 (1H, s)

Preparation 40

To a suspension of 5-chloromethylthio-1-trityl-1H-1,2,3-triazole (10.97 g) in acetone (150 ml) was added sodium iodide (8.4 g) at room temperature, and then it was stirred at 50°C for 3 hours. After it was poured into ethyl acetate (300 ml) and water (300 ml), the organic layer was separated, dried over magnesium sulfate, and evaporated. 60% sodium hydride (1.10 g) was added to a solution of N-hydroxyphthalimide (4.49 g) in N,N-dimethylformamide (45 ml) at room temperature, it was stirred at the same temperature for 30 minutes. The above residue was added thereto, the reaction mixture was stirred at 50°C for one hour. After it was poured into ethyl acetate (250 ml) and water (300 ml), the organic layer was separated, dried over magnesium sulfate, and evaporated. To the residue

diisopropyl ether (15 ml) was added, the resulting precipitate was collected by filtration. N-(1-trityl-1H-1,2,3-triazol-5-yl)thiomethoxyphthalimide (5.6 g) was obtained.

NMR (DMSO-d_6, δ) : 5.62 (2H, s), 6.95-7.02 (6H, m), 7.38-7.45 (9H, m), 7.80 (4H, s), 8.04 (1H, s)

MS (FAB) m/z : 519 (M^++1)

Preparation 41

(Z)-2-(2-Formylamino-5-bromothiazol-4-yl)-2-(1-trityl-1H-1,2,3-triazol-5-yl)thiomethoxyiminoacetic acid was obtained according to a similar manner to that of Preparation 3.

NMR (DMSO-d_6, δ) : 5.62 (2H, s), 6.98-7.04 (6H, m), 7.30-7.40 (9H, m), 7.85 (1H, s), 8.56 (1H, s)

MS (FAB) m/z : 650 (M^++1)

Preparation 42

Methanesulfonyl chloride (15.4 g) was added to an ice-cooling solution of 4-hydroxymethyl-1-methylpyrazole (10 g) and triethylamine (19.8 g) in dichloromethane (100 ml), and the mixture was stirred at 5-10°C for two hours. After it was poured into ice-water (150 ml), organic layer was separated, dried over magnesium sulfate, and evaporated. On the other hand, N-hydroxyphthalimide (12.5 g) and triethylamine (8.57 g) was dissolved in N,N-dimethylformamide (160 ml), thereto was added the above residue at room temperature. The reaction mixture was warmed at 60°C, and it was stirred at the same temperature for 2 hours. The solution was poured into ethyl acetate (500 ml) and water (500 ml), and then the organic layer was separated, dried over magnesium sulfate, and evaporated. N-(1-Methylpyrazol-4-yl)methoxyphthalimide (11.3 g) was obtained.

NMR (DMSO-d_6, δ) : 3.81 (3H, s), 5.04 (2H, s), 7.50 (1H, s), 7.85 (5H, s)

MS m/z : 258 (M^++1)

Preparation 43

(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(1-methylpyrazol-4-yl)methoxyiminoacetic acid (1.15 g) was obtained according to a similar manner to that of Preparation 3.

NMR (DMSO-d_6, δ) : 3.82 (3H, s), 5.03 (2H, s), 7.47 (1H, s), 7.75 (1H, s), 8.54 (1H, s), 12.8 (1H, s)

MS (FAB) m/z : 344 (M^++1)

Preparation 44

To a solution of 4-hydroxymethylpyrazole (5.0 g) in tetrahydrofuran (50 ml) was added di-tert-butyl dicarbonate (11.1 g) and 4-dimethylaminopyridine (20 mg). It was warmed at 50°C for 2 hours. The reaction mixture was concentrated, and subjected to column chromatography (70 g). It was eluted with ethyl acetate. The active fractions were collected, concentrated to give 1-tert-butoxycarbonyl-4-hydroxymethylpyrazole (7.9 g)

NMR (DMSO-d_6, δ) : 1.57 (9H, s), 4.38 (2H, d, J=5.4Hz), 5.04 (1H, t, J=5.4Hz), 7.73 (1H, s), 8.08 (1H, s)

MS m/z : 199 (M^++1)

Preparation 45

N-(1-tert-Butoxycarbonylpyrazol-4-yl)methoxyphthalimide was obtained according to a similar manner to that of Preparation 42.

NMR (DMSO-d_6, δ) : 1.57 (9H, s), 5.12 (2H, s), 7.86 (4H, s), 7.92 (1H, s), 8.43 (1H, s)

MS m/z : 344 (M^++1)

Preparation 46

(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(1-tert-butoxycarbonylpyrazol-4-yl)methoxyiminoacetic acid was

obtained according to a similar manner to that of Preparation 3.

NMR (DMSO-d_6, δ) : 1.58 (9H, s), 5.13 (2H, s), 7.85 (1H, s), 8.33 (1H, s), 8.54 (1H, s)

MS (FAB) m/z : 429 (M^+)

Preparation 47

(Z)-2-(2-Formylaminothiazol-4-yl)-2-(3-cyclopentenyl)-oxyiminoacetic acid (15.0 g) was suspended into methanol (150 ml), and N-bromosuccinimide (10.5 g) was added thereto with ice-cooling. After the reaction mixture was stirred at room temperature for 2 hours, it was concentrated to 70 ml. The solution was poured into ethyl acetate (300 ml) and water (300 ml), and then it was adjusted to pH 3.0 with sodium hydrogen carbonate. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated. (Z)-2-(2-Formylamino-5-bromothiazol-4-yl)-2-(3-cyclopentenyl) oxyiminoacetic acid (8.1 g) was obtained.

IR (KBr) : 3159, 3080, 2800, 1774, 1697, 1639, 1192 cm^{-1}

NMR (DMSO-d_6, δ) : 1.80-2.50 (4H, m), 5.29 (1H, m), 5.90 (1H, m), 6.13 (1H, m), 8.05 (1H, m)

MS (FAB) m/z : 360 (M^+)

Preparation 48

(Z)-2-(2-Aminothiazol-4-yl)-2-ethoxyiminoacetic acid (7.0 g) was suspended into methanol (105 ml), and N-iodosuccinimide (8.1 g) was added thereto with ice-cooling. After the reaction mixture was stirred at room temperature for an hour, ethyl acetate (100 ml) was added thereto, and the resulting precipitate was collected by filtration. (Z)-2-(2-Amino-5-iodothiazol-4-yl)-2-ethoxyiminoacetic acid (3.8 g) was obtained.

IR (KBr) : 1709, 1645, 1599, 1041 cm^{-1}

NMR (DMSO-d_6, δ) : 1.28 (3H, t, J=7.0Hz), 4.14 (2H, q, J=7.0Hz), 7.43 (2H, s), 11.07 (1H, s)

The following compounds (Preparations 49 and 50) were obtained according to a similar manner to that of Preparation 48.

Preparation 49

(Z)-2-(2-Amino-5-bromothiazol-4-yl)-2-ethoxyiminoacetic acid

IR (KBr) : 1705, 1643, 1595, 1568 cm^{-1}

NMR (DMSO-d_6, δ) : 1.24 (3H, t, J=7.0Hz), 4.14 (2H, q, J=7.0Hz), 7.86 (2H, br)

MS (FAB) m/z : 294 (M^+), 296 (M^++2)

Preparation 50

(Z)-2-(2-Amino-5-iodothiazol-4-yl)-2-acetoxyiminoacetic acid

NMR (DMSO-d_6, δ) : 2.24 (3H, s), 7.55 (2H, s)

Preparation 51

(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(1-tritylimidazol-4-yl)methoxyiminoacetic acid was obtained according to a similar manner to that of Preparation 3

NMR (DMSO-d_6, δ) : 5.05 (2H, s), 6.95 (1H, s), 7.25-7.40 (16H, m), 8.54 (1H, s), 12.86 (1H, br s)

Preparation 52

Methyl (Z)-2-(2-tert-butoxycarbonylamino-5-chlorothiazol-4-yl)-2-pentenoate was obtained according to a similar manner to that of Preparation 13.

NMR ($CDCl_3$, δ) : 1.10 (3H, t, J=7.5Hz), 1.52 (9H, s), 2.47 (2H, qin, J=7.5Hz), 3.78 (3H, s), 6.56 (1H, t, J=7.5Hz)

Preparation 53

To a solution of methyl (Z)-2-(2-tert-butoxycarbonylamino-5-chlorothiazol-4-yl)-2-pentenoate (3 g)

in 2-propanol (9 ml) was added 1N-sodium hydroxide solution (27 ml) under at 30°C. The stirring was continued for 3 hours at the same temperature. The reaction mixture was poured into a mixture of ethyl acetate (200 ml) and water (50 ml). The separated organic phase was washed with brine (100 ml) and dried over magnesium sulfate and evaporated in vacuo to give (Z)-2-(2-tert-butoxycarbonylamino-5-chlorothiazol-4-yl)-2-pentenoic acid (1.7 g).

NMR (DMSO-d_6, δ) : 1.07 (3H, t, J=7.5Hz), 1.47 (9H, s), 2.44 (2H, qin, J=7.5Hz), 6.38 (1H, t, J=7.5Hz)

Preparation 54

Ethyl (Z)-2-(2-tert-butoxycarbonylamino-5-chlorooxazol-4-yl)-2-ethoxyiminoacetate was obtained according to a similar manner to that of Preparation 13.

NMR (DMSO-d_6, δ) : 1.15-1.35 (6H, m), 1.42 (9H, s), 4.23 (2H, q, J=7.0Hz), 4.32 (2H, q, J=7.1Hz)

Preparation 55

To a solution of ethyl (Z)-2-(2-tert-butoxycarbonylamino-5-chlorooxazol-4-yl)-2-ethoxyiminoacetate (1.85 g) in dichloromethane (5.6 ml) and anisole (1.85 ml) was added dropwise trifluoroacetic acid (3.7 ml) at 20°C. The stirring was continued for 2 hours at 30°C. The reaction mixture was poured into isopropyl ether (100 ml). The resulting powder was collected by filtration, and dried in vacuo to give ethyl (Z)-2-(2-amino-5-chlorooxazol-4-yl)-2-ethoxyiminoacetate (930 mg).

NMR (DMSO-d_6, δ) : 1.05-1.35 (6H, m), 4.10-4.4 (4H, m), 7.25 (2H, br s)

MS (APCI) m/z : 262 $(M+H)^+$

Preparation 56

(Z)-2-(2-Amino-5-chlorooxazol-4-yl)-2-ethoxyiminoacetic acid was obtained according to a similar manner to that of

Preparation 31.

NMR (DMSO-d_6, δ) : 1.10-1.40 (6H, m), 4.00-4.40 (4H, m), 7.02 (2H, br s)

MS (APCI) m/z : 234 $(M+H)^+$

The following compounds (Examples 9 to 21) were obtained according to a similar manner to that of Example 3.

Example 9

7β-[(Z)-2-(2-Amino-5-fluorothiazol-4-yl)-2-ethoxyimino-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1614, 1535, 1353, 1220, 1062 cm^{-1}

NMR (DMSO-d_6, δ) : 1.20 (3H, t, J=7Hz), 2.93 and 3.19 (2H, ABq, J=17Hz), 3.50-3.70 (2H, m), 4.07 (2H, q, J=7Hz), 4.15-4.55 (2H, m), 5.00 (1H, d, J=5Hz), 5.05 and 5.22 (2H, ABq, J=18Hz), 5.60 (1H, dd, J=5Hz, 8Hz), 5.81 (1H, d, J=3Hz), 7.12 (2H, br s), 7.28 (2H, br s), 8.10 (1H, d, J=3Hz), 9.50 (1H, d, J=8Hz)

MS (FAB) m/z : 555 (M^+)

Example 10

7β-[(Z)-2-(2-Amino-5-bromothiazol-4-yl)-2-(2-fluoroethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1666, 1639, 1614, 1535, 1392 cm^{-1}

NMR (DMSO-d_6, δ) : 2.89 and 3.20 (2H, ABq, J=17Hz), 3.40-3.65 (2H, m), 4.05-4.55 (2H+2H, m), 4.55-4.95 (2H, m), 5.00 (1H, d, J=5Hz), 5.05 and 5.21 (2H, ABq, J=18Hz), 5.60 (1H, dd, J=5Hz, 8Hz), 5.81 (1H, d, J=3Hz), 7.27 (2H, br s), 7.42 (2H, br s), 8.10 (1H, d, J=3Hz), 9.52 (1H, d, J=8Hz)

Example 11

7β-[(Z)-2-(2-Amino-5-bromothiazol-4-yl)-2-(methylthiomethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1612, 1537, 1351, 1218, 1064 cm^{-1}

NMR (DMSO-d_6, δ) : 2.21 (3H, s), 2.90 and 3.17 (2H, ABq, J=17Hz), 3.40-3.65 (2H, m), 4.23-4.60 (2H, m), 5.00 (1H, d, J=5Hz), 5.05-5.25 (2H+2H, m), 5.69 (1H, dd, J=5Hz, 8Hz), 5.81 (1H, d, J=3Hz), 7.28 (2H, br s), 7.45 (2H, br s), 8.10 (1H, d, J=3Hz), 9.56 (1H, d, J=8Hz)

Example 12

7β-[(Z)-2-(2-tert-Butoxycarbonylamino-5-chlorothiazol-4-yl)-2-pentenoylamino]-3-[1-(2-hydroxyethyl)-5-amino-2-pyrazolio]methyl-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 1.01 (3H, t, J=7.5Hz), 1.46 (9H, s), 2.10-2.30 (2H, m), 3.10-3.30 (2H, m), 3.30-3.70 (2H, m), 4.00-4.45 (2H, m), 5.10-5.40 (3H, m), 5.80-5.95 (2H, m), 6.37 (1H, t, J=7.5Hz), 7.32 (2H, br s), 8.08 (1H, d, J=3.1Hz), 9.30 (1H, d, J=8.0Hz)

Example 13

7β-[(Z)-2-(2-Amino-5-chlorooxazol-4-yl)-2-ethoxyimino-acetamido] -3-[1-(2-hydroxyethyl)-5-amino-2-pyrazolio]-methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1668, 1602, 1585, 1392, 1043 cm^{-1}

NMR (DMSO-d_6, δ) : 1.21 (3H, t, J=7.0Hz), 3.00 and 3.23 (2H, ABq, J=17.3Hz), 3.35-3.80 (2H, m), 4.06 (2H, q, J=7.0Hz), 4.20-4.55 (2H, m), 5.06 (1H, d, J=5.0Hz), 5.0-5.45 (2H, m), 5.66 (1H, dd, J=8.4Hz, 5.0Hz), 5.83 (1H, d, J=3.1Hz), 7.15 (2H, br s), 7.28 (2H, br s), 8.08 (1H, d, J=3.1Hz), 9.57 (1H, d, J=8.4Hz)

Example 14

7β-[(Z)-2-tert-Butoxycarbonylmethoxyimino-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

MS (FAB) m/z : 684.9 (M^+)

Example 15

7β-[(Z)-2-Carbamoylmethoxyimino-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

MS (FAB) m/z : 628.2 (M^+), 630.2 (M^++2)

Example 16

7β-[(Z)-2-(1-tert-Butoxycarbonyl-1-methylethoxyimino)-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1788, 1643 cm^{-1}

MS (FAB) m/z : 685.1 (M^+), 687.2 (M^++2)

Example 17

7β-[(Z)-2-(3-tert-Butoxycarbonylallyloxyimino)-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1749, 1684, 1649, 1541 cm^{-1}

MS (FAB) m/z : 711.0 (M^+), 713.2 (M^++2)

Example 18

7β-[(Z)-2-Ethoxyimino-2-(2-amino-5-methylthiazol-4-yl)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 3336, 1772, 1649, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 1.22 (3H, t, J=7.0Hz), 2.33 (3H, s), 3.18, 2.91 (2H, ABq, J=17.0Hz), 3.5-3.7 (2H, m), 4.07 (2H, q, J=7.0Hz), 4.2-4.6 (2H, m), 4.99 (1H, d, J=4.8Hz), 5.21, 5.04 (2H, ABq, J=15Hz), 5.59 (1H, dd, J=8.6Hz, 4.8Hz), 5.81 (1H, d, J=3.1Hz),

6.90 (2H, br s), 7.27 (2H, br s), 8.10 (1H, d, J=3.1Hz), 9.34 (1H, d, J=8.6Hz)

MS (FAB) m/z : 551.0 (M^++1)

Example 19

7β-[(Z)-2-Trityloxyimino-2-(2-tritylamino-5-methylthiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1792, 1774 cm^{-1}

MS (FAB) m/z : 1007.3 (M^+)

Example 20

7β-[(Z)-2-Methoxyimino-2-(2-amino-5-methylthiazol-4-yl, acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1649, 1614, 1045 cm^{-1}

NMR (DMSO-d_6, δ) : 2.33 (3H, s), 2.91, 3.19 (ABq, 2H, J=17.4Hz), 3.5-3.7 (2H, m), 3.81 (3H, s), 4.2-4.6 (2H, m), 4.99 (1H, d, J=4.8Hz), 5.04, 5.21 (2H, ABq, J=15.3Hz), 5.59 (1H, dd, J=8.6Hz, 4.8Hz), 5.82 (1H, d, J=3.2Hz), 6.91 (2H, br s), 7.33 (2H, br s), 8.10 (1H, d, J=3.2Hz), 9.37 (1H, d, J=8.6Hz)

MS (FAB) m/z : 537.2 (M^++1)

Example 21

7β-[(Z)-2-Methoxyimino-2-(2-formylamino-5-cyanothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]-methyl-3-cephem-4-carboxylate

MS (FAB) m/z : 576.1 (M^++1)

Example 22

To a solution of phosphorus pentachloride (2.3 g) in 40 ml of dichloromethane, (Z)-2-difluoromethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetic acid (2.0 g) was added at -30°C and stirred at -15°C for 2 hours to generate acid chloride in

situ. A solution of 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (2.77 g) and N-(trimethylsilyl)acetamide (9.66 g) in 28 ml of N,N-dimethylformamide and 28 ml of tetrahydrofuran was added to the acid chloride solution at 0°C. After 3 hours, the reaction mixture was dropped into 600 ml of ethyl acetate to get precipitates, which were purified by column chromatography on HP-20 resin and preparative HPLC to get 57 mg of 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 1774, 1668, 1639, 1614 cm^{-1}

NMR (DMSO-d_6, δ) : 2.91, 3.20 (2H, ABq, J=17.3Hz), 3.4-3.9 (2H, m), 4.2-4.6 (2H, m), 5.03 (1H, d, J=4.9Hz), 5.06, 5.21 (2H, ABq, J=15.1Hz), 5.61 (1H, dd, J=8.2Hz, 4.9Hz), 5.81 (1H, d, J=3.1Hz), 7.12 (1H, t, J=70.8Hz), 7.28 (2H, br s), 7.54 (2H, br s), 8.10 (1H, d, J=3.1Hz), 9.87 (1H, d, J=8.2Hz),

MS (FAB) m/z : 593.0 (M^+)

Example 23

7β-[(Z)-2-(5-Chloro-2-formylaminothiazol-4-yl)-2-(fluoromethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate was obtained according to a similar manner to that of Example 22.

NMR (DMSO-d_6, δ) : 2.94, 3.25 (2H, ABq, J=17.4Hz), 3.5-3.8 (2H, m), 4.2-4.6 (2H, m), 5.06 (1H, d, J=4.8Hz), 5.08, 5.21 (2H, ABq, J=15.4Hz), 5.67 (1H, dd, J=8.4Hz, 4.8Hz), 5.77 (2H, d, J=53.7Hz), 5.83 (1H, d, J=3.1Hz), 7.31 (2H, br s), 8.09 (1H, d, J=3.1Hz), 8.55 (1H, s), 9.81 (1H, d, J=8.4Hz)

MS (FAB) m/z : 603.0 (M^+)

Example 24

Phosphorus pentachloride (2.48 g) was suspended into dichloromethane (19 ml), and then it was cooled to -20°C, and (Z)-2-(2-amino-5-iodothiazol-4-yl)-2-ethoxyiminoacetic acid (3.7 g) was added thereto. After it was stirred at -15°C for 2 hours, diisopropyl ether (20 ml) was added thereto, and the resulting precipitate was collected by filtration (Precipitate A). On the other hand, 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate monohydrochloride (3.57 g) was suspended into ethyl acetate (20 ml) and N,N-dimethylformamide (30 ml), and then N-trimethylsilylacetamide (11.4 g) was added thereto. It was warmed at 35°C with stirring for 10 minutes to give a clear solution. The precipitate A which was synthesized before was added to this solution with stirring at 5°C, then it was stirred at the same temperature for an hour. After that, the reaction mixture was poured into a mixed solution of ethyl acetate (250 ml), diisopropyl ether (50 ml), and methanol (7 ml). The resulting precipitate was collected by filtration, and it was dissolved into water (100 ml) at pH 6.5. After the solution was adjusted to pH 4.0 with 1N-hydrochloric acid, it was subjected to column chromatography on Diaion HP-20 (90 ml) [Trademark; Mitsubishi Kasei Co.]. The column was washed with water (500 ml), and the object compound was eluted with 40% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7β-[(Z)-2-(2-amino-5-iodothiazol-4-yl)-2-ethoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.47 g).

IR (KBr) : 1774, 1614, 1529, 1039 cm^{-1}

NMR (DMSO-d_6, δ) : 1.29 (3H, t, J=7.0Hz), 2.93, 3.19 (2H, ABq, J=17Hz), 3.40-3.70 (2H, m), 4.12 (2H, q, J=7.0Hz), 4.20-4.60 (2H, m), 5.00 (1H, d, J=4.8Hz), 5.05, 5.22, (2H, ABq, J=15Hz), 5.60 (1H, dd, J=4.8Hz, 8.5Hz), 5.82 (1H, d, J=3.2Hz), 7.27 (2H, s), 7.38 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.42 (1H,

d, J=8.5Hz)

MS (FAB) m/z : 663 (M^++1)

The following compounds (Examples 25 to 28) were obtained according to a similar manner to that of Example 24.

Example 25

7β-[(Z)-2-(2-Amino-5-bromothiazol-4-yl)-2-ethoxyimino-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1666, 1649, 1614, 1537, 1041 cm^{-1}

NMR (DMSO-d_6, δ) : 1.25 (3H, t, J=7.0Hz), 2.93, 3.20 (2H, ABq, J=17Hz), 3.50-3.80 (2H, m), 4.11 (2H, q, J=7.0Hz), 4.20-4.60 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.12, 5.21 (2H, ABq, J=15Hz), 5.59 (1H, dd, J=4.9Hz, 8.4Hz), 5.81 (1H, d, J=3.2Hz), 7.23 (2H, s), 7.38 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.43 (1H, d, J=8.4Hz)

MS (FAB) m/z : 615 (M^+), 617 (M^++2)

Example 26

7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-ethoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1612, 1539, 1038 cm^{-1}

NMR (DMSO-d_6, δ) : 1.23 (3H, t, J=7.0Hz), 2.93, 3.19 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 4.10 (2H, q, J=7.0Hz), 4.20-4.60 (2H, m), 5.01 (1H, d, J=4.9Hz), 5.05, 5.22 (2H, ABq, J=15Hz), 5.60 (1H, dd, J=4.9Hz, 8.5Hz), 5.82 (1H, d, J=3.2Hz), 7.27 (2H, s), 7.37 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.46 (1H, d, J=8.5Hz)

MS (FAB) m/z : 571 (M^+)

Example 27

7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-

methoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1653, 1610, 1579, 1539, 1049 cm^{-1}

NMR (DMSO-d_6, δ) : 2.92, 3.20 (2H, ABq, J=17Hz), 3.4-3.8 (2H, m), 3.84 (3H, s), 4.2-4.6 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.05, 5.21 (2H, ABq, J=15Hz), 5.60 (1H, dd, J=4.9Hz, 8.5Hz), 5.82 (1H, d, J=3.2Hz), 7.28 (2H, s), 7.41 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.52 (1H, d, J=8.5Hz)

MS (FAB) m/z : 557 (M^+)

Example 28

7β-[(Z)-2-(2-Amino-5-methylthiothiazol-4-yl)-2-methoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1649, 1614, 1537, 1525, 1041 cm^{-1}

NMR (DMSO-d_6, δ) : 2.38 (3H, s), 2.93, 3.20 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 3.84 (3H, s), 4.20-4.60 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.05, 5.22 (2H, ABq, J=16Hz), 5.60 (1H, dd, J=4.9Hz, 8.5Hz), 5.82 (1H, d, J=3.2Hz), 7.26 (2H, s), 7.32 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.41 (1H, d, J=8.5Hz)

MS (FAB) m/z : 569 (M^++1)

The following compounds (Examples 29 to 32) were obtained according to a similar manner to that of Example 1.

Example 29

7β-[(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-propargyloxyimino)acetamido]-3-[5-amino-1-[2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.15-3.45 (2H+1H, m), 3.50-3.65 (2H, m), 4.10-4.45 (2H, m), 4.65-4.70 (2H, m), 5.00-5.35 (2H, m), 5.07 (1H, d, J=4.9Hz), 5.81 (1H, dd, J=4.9Hz, 8.4Hz), 5.85 (1H, d, J=3.2Hz), 8.00 (1H,

d, J=3.2Hz), 8.48 (1H, s), 9.73 (1H, d, J=8.4Hz), 12.87 (1H, br s)

Example 30

7β-[(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(methylthiomethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 2.10 (3H, s), 3.2-3.4 (2H, m), 4.05-4.50 (2H, m), 5.00-5.40 (2H+2H, m), 5.18 (1H, d, J=4.9Hz), 5.85 (1H, dd, J=4.9Hz, 8.4Hz), 5.90 (1H, d, J=3.1Hz), 8.12 (1H, d, J=3.1Hz), 8.52 (1H, s), 9.65 (1H, d, J=8.4Hz), 12.9 (1H, br s)

Example 31

7β-[2-(2-Formylamino-5-chlorothiazol-4-yl)-2-oxoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]-methyl-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.20-3.40 (2H, m), 2.45-2.60 (2H, m), 4.20-4.45 (2H, m), 5.10-5.40 (2H+1H, m), 5.75-5.85 (1H+1H, m), 8.89 (2H, br s), 7.97 (1H, d, J=2.9Hz), 8.53 (1H, s), 9.84 (1H, d, J=7.9Hz), 13.00 (1H, s)

Example 32

7β-[(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(1-tritylimidazol-4-yl)methoxyiminoacetamido]-3-[1-(2-hydroxyethyl)-5-amino-2-pyrazolio]methyl-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.0-3.40 (2H, m), 3.50-3.75 (2H, m), 4.0-4.50 (2H, m), 5.05-5.40 (5H, m), 5.80-5.95 (2H, m), 7.14 (1H, s), 7.30-7.60 (18H, m), 8.03 (1H, d, J=3.1Hz), 8.54 (1H, s), 9.74 (1H, d, J=8.4Hz), 12.9 (1H, br s)

The following compounds (Examples 33 to 34) were

obtained according to a similar manner to that of Example 2.

Example 33

7β-[(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(2-acetoxyethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1776, 1726, 1673, 1631, 1542, 1390, 1280, 1064 cm^{-1}

NMR (DMSO-d_6, δ) : 2.00 (3H, s), 3.00-3.40 (2H, m), 3.45-3.65 (2H, m), 4.10-4.50 (2H+2H+2H, m), 5.05 (1H, d, J=4.9Hz), 5.00-5.30 (2H, m), 5.68 (1H, dd, J=4.9Hz, 7.9Hz), 5.83 (1H, d, J=2.8Hz), 7.32 (2H, br s), 8.09 (1H, d, J=2.8Hz), 8.53 (1H, s), 9.62 (1H, d, J=7.9Hz)

Example 34

7β-[(Z)-2-(2-Formylamino-5-fluorothiazol-4-yl)-2-formyloxyimino)acetamido]-3-(5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.25-3.55 (2H, m), 3.60-3.70 (2H, m), 5.05-5.50 (1H+2H, m), 5.75 (1H, dd, J=5Hz, 7.9Hz), 5.91 (1H, d, J=3Hz), 7.48 (2H, br s), 7.95 (1H, s), 7.98 (1H, d, J=3Hz), 8.47 (1H, s), 9.75 (1H, d, J=7.9Hz)

The following compounds (Examples 35 to 38) were obtained according to a similar manner to that of Example 5.

Example 35

7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-(propargyloxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1639, 1614, 1540, 1324, 1025 cm^{-1}

NMR (DMSO-d_6, δ) : 2.89 and 3.20 (2H, ABq, J=17.3Hz); 3.35-3.45 (1H, m), 3.45-3.65 (2H, m), 4.20-4.60

(2H, m), 4.60-4.80 (2H, m), 5.00 (1H, d, J=4.8Hz), 5.05 and 5.18 (2H, ABq, J=18.4Hz), 5.60 (1H, dd, J=4.8Hz, 8.3Hz), 5.81 (1H, d, J=3.2Hz), 7.19 (2H, br s), 7.39 (2H, br s), 8.09 (1H, d, J=3.2Hz), 9.55 (1H, d, J=8.3Hz)

Example 36

7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-(methylthiomethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1614, 1538, 1390, 1355, 1062 cm^{-1}

NMR (DMSO-d_6, δ) : 2.20 (3H, s), 2.92 and 3.19 (2H, ABq, J=17.3Hz), 3.45-3.65 (2H, m), 4.20-4.55 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.05-5.30 (2H, m), 5.25 (2H, s), 5.60 (1H, dd, J=4.9Hz, 8.3Hz), 5.82 (1H, d, J=3.2Hz), 7.30 (2H, br s), 7.40 (2H, br s), 8.09 (1H, d, J=3.2Hz), 9.56 (1H, d, J=8.3Hz)

Example 37

7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-oxo-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1668, 1614, 1538, 1390, 1353, 1062 cm^{-1}

NMR (DMSO-d_6, δ) : 2.98 and 3.23 (2H, ABq, J=17.2Hz), 3.25-3.65 (2H, m), 4.15-4.55 (2H, m), 5.04 (1H, d, J=4.9Hz), 5.07 and 5.25 (2H, ABq, J=18.2Hz), 5.63 (1H, dd, J=4.9Hz, 7.9Hz), 5.82 (1H, d, J=2.8Hz), 7.30 (2H, br s), 7.58 (2H, br s), 8.09 (1H, d, J=2.8Hz), 9.68 (1H, d, J=7.9Hz)

Example 38

7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-(imidazol-4-yl)methoxyiminoacetamido]-3-[1-(2-hydroxyethyl)-5-amino-2-pyrazolio]methyl-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 2.89 and 3.17 (2H, ABq, J=17.7Hz),

3.40-3.70 (2H, m), 4.20-4.55 (2H, m), 4.90-5.30 (5H, m), 5.60 (1H, dd, J=8.4Hz, 4.8Hz), 5.82 (1H, d, J=3.1Hz), 7.08 (1H, s), 7.27 (2H, br s), 7.35 (2H, br s), 7.57 (1H, s), 8.09 (1H, d, J=3.1Hz), 9.64 (1H, d, J=8.4Hz)

MS (FAB) m/z : 624 $(M+H)^+$

The following compounds (Examples 39 to 43) were obtained according to a similar manner to that of Example 7.

Example 39

7β-[(Z)-2-tert-Butoxycarbonylmethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

MS (FAB) m/z : 657.1 (M^+)

Example 40

7β-[(Z)-2-Carbamoylmethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1676, 1616, 1539 cm^{-1}

NMR (DMSO-d_6, δ) : 2.89, 3.19 (2H, ABq, J=17.4Hz), 3.59 (2H, br s), 4.2-4.6 (2H, m), 4.67 (2H, s), 5.00 (1H, d, J=4.9Hz), 5.06, 5.20 (2H, ABq, J=15Hz), 5.62 (1H, dd, J=8.6Hz, 4.9Hz), 5.81 (1H, d, J=3.1Hz), 7.26 (2H, br s), 7.41 (2H, br s), 8.10 (1H, d, J=3.1Hz), 9.45 (1H, d, J=8.6Hz)

Example 41

7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1668, 1639, 1614 cm^{-1}

NMR (DMSO-d_6, δ) : 2.88, 3.21 (2H, ABq, J=17.3Hz), 3.5-3.7 (2H, m), 4.2-4.6 (2H, m), 5.01 (1H, d,

J=4.9Hz), 5.07, 5.18 (2H, ABq, J=15.2Hz), 5.60 (1H, dd, J=8.3Hz, 4.9Hz), 5.71 (1H, d, J=56.1Hz), 5.81 (1H, d, J=3.2Hz), 7.22 (2H, br s), 7.48 (2H, br s), 8.10 (1H, d, J=3.2Hz), 9.72 (1H, d, J=8.3Hz)

MS (FAB) m/z : 575.0 (M^+)

Example 42

7β-[(Z)-2-Hydroxyimino-2-(2-amino-5-methylthiazol-4-yl)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 3332, 1770, 1649, 1618 cm^{-1}

NMR (DMSO-d_6, δ) : 2.32 (3H, s), 2.88, 3.16 (2H, ABq, J=17.5Hz), 3.5-3.7 (2H, m), 4.2-4.5 (2H, m), 4.99 (1H, d, J=4.9Hz), 5.04, 5.21 (2H, ABq, J=15.2Hz), 5.61 (1H, dd, J=8.6Hz, 4.9Hz), 5.81 (1H, d, J=3.2Hz), 6.81 (2H, br s), 7.30 (2H, br s), 8.09 (1H, d, J=3.2Hz), 9.19 (1H, d, J=8.6Hz)

MS (FAB) m/z : 523.1 (M^++1)

Example 43

7β-[(Z)-2-Methoxyimino-2-(2-amino-5-cyanothiazol-4-yl)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 3390, 2210, 1772, 1649, 1618 cm^{-1}

NMR (DMSO-d_6, δ) : 2.92, 3.22 (2H, ABq, J=17.3Hz), 3.5-3.7 (2H, m), 3.91 (3H, s), 4.2-4.6 (2H, m), 5.01 (1H, d, J=4.9Hz), 5.07, 5.21 (2H, ABq, J=15.1Hz), 5.60 (1H, dd, J=8.6Hz, 4.9Hz), 5.82 (1H, d, J=3.1Hz), 7.30 (2H, br s), 8.11 (1H, d, J=3.1Hz), 8.34 (2H, br s), 9.61 (1H, d, J=8.6Hz)

MS (FAB) m/z : 548.0 (M^++1)

Example 44

To a suspension of 7β-[(Z)-2-(2-tert-butoxycarbonylamino-5-chlorothiazol-4-yl)-2-pentenoylamino]-

3-[1-(2-hydroxyethyl)-5-amino-2-pyrazolio]methyl-3-cephem-4-carboxylate (750 mg) in dichloromethane (2.4 ml) and anisole (0.75 ml) was added dropwise trifluoroacetic acid (1.5 ml) at 20°C. The stirring was continued for 2 hours at the room temperature. The reaction mixture was poured into isopropyl ether (30 ml). The resulting powder was collected by filtration and dried in vacuo. The powder was dissolved in a water (50 ml), adjusted to pH 3.0 with aqueous sodium hydrogencarbonate and then subjected to column chromatography on HP-20 (30 ml) and eluted with 20% aqueous isopropyl alcohol. And then active fraction was lyophilized to give 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-pentenoylamino]-3-[1-(2-hydroxyethyl)-5-amino-2-pyrazolio]methyl-3-cephem-4-carboxylate (60 mg).

NMR (DMSO-d_6, δ) : 0.98 (3H, t, J=7.5Hz), 2.2 (2H, qin, J=7.5Hz), 2.93 and 3.20 (2H, ABq, J=17.9Hz), 3.40-3.70 (2H, m), 4.20-4.60 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.05 and 5.20 (2H, ABq, J=15.8Hz), 5.58 (1H, dd, J=4.9Hz, 8.0Hz), 5.80 (1H, d, J=3.1Hz), 6.28 (1H, t, J=7.5Hz), 7.20 (2H, br s), 7.24 (2H, br s), 8.10 (1H, d, J=3.1Hz), 9.16 (1H, d, J=8.0Hz)

Example 45

A solution of 7β-[(Z)-2-(3-tert-butoxycarbonylallyloxyimino)-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.48 g) in 1.5 ml of dichloromethane and 0.5 ml of anisole was treated with 1 ml of trifluoroacetic acid. After 4 hours, the reaction mixture was poured into isopropyl ether. The precipitates were solved in 4 ml of methanol, and treated with hydrochloric acid (0.28 ml), and stirred for 4 hours at room temperature. The reaction mixture was dropped into ethyl acetate to get precipitates, which were purified by preparative HPLC to get 28 mg of 7β-[(Z)-2-((E)-3-

carboxyallyloxyimino)-2-(2-amino-5-chlorothiazol-4-yl)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 1772, 1651, 1541 cm^{-1}

NMR (DMSO-d_6, δ) : 2.89, 3.19 (2H, ABq, J=16.9Hz), 3.5-3.7 (2H, m), 4.2-4.6 (2H, m), 4.76 (2H, d, J=2Hz), 5.01 (1H, d, J=4.9Hz), 5.07, 5.21 (2H, ABq, J=15Hz), 5.61 (1H, dd, J=8.5Hz, 4.9Hz), 5.81 (1H, d, J=3.2Hz), 5.99 (1H, d, J=15.8Hz), 6.84 (1H, dt, J=15.8Hz, 2Hz), 7.26 (2H, br s), 7.41 (2H, br s), 8.10 (1H, d, J=3.2Hz), 9.62 (1H, d, J=8.5Hz)

MS (FAB) m/z : 627.0 (M^+)

Example 46

To a suspension of 7β-[(Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-(2-acetoxyethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (1.2 g) in methanol (12 ml) was added concentrated hydrochloric acid (0.86 ml) under stirring at 25°C to 30°C. The stirring was continued for 3 hours at the 20°C to 30°C. The reaction mixture was poured into a cooled water (100 ml), and adjusted to pH 3.5 with aqueous sodium hydrogen carbonate. To the resulting solution was evaporated in vacuo by removal of methanol. The residue was added 3N-sodium hydroxide solution (3 ml) under ice-cooling with stirring and the mixture was stirred for 30 minutes at 5°C. The reaction mixture was adjusted to pH 3.5 with 6N-hydrochloric acid. The residue was subjected to column chromatography on HP-20 (50 ml), and eluted with 15% 2-propanol and the eluate was lyophilized to give 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(2-hydroxyethoxyimino)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (250 mg).

IR (KBr) : 1774, 1648, 1612, 1538, 1390, 1355, 1218, 1066 cm^{-1}

NMR (DMSO-d_6, δ) : 2.94 and 3.18 (2H, ABq, J=17.3Hz), 3.40-3.65 (2H+2H, m), 4.00-4.20 (2H, m), 4.20-4.65 (2H+1H, m), 5.01 (1H, d, J=4.9Hz), 5.04 and 5.22 (2H, ABq, J=18.2Hz), 5.62 (1H, dd, J=4.9Hz, 7.9Hz), 5.81 (1H, d, J=2.9Hz), 7.26 (2H, br s), 7.40 (2H, br s), 8.10 (1H, d, J=2.9Hz), 9.43 (1H, d, J=7.9Hz)

Example 47

To a suspension of 7β-[(Z)-2-(2-formylamino-5-fluorothiazol-4-yl)-2-formyloxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (562 mg) in methanol (5.6 ml) was added concentrated hydrochloric acid (0.9 ml) under stirring at 25°C to 30°C. The stirring was continued for 3 hours at 20°C to 30°C. The reaction mixture was poured into an ice-cooled water (100 ml), and adjusted to pH 4.0 with aqueous sodium hydrogen carbonate. The resulting solution was evaporated in vacuo. The residue was subjected to column chromatography on HP-20 (50 ml), and eluted with 15% 2-propanol and the eluate was lyophilized to give 7β-[(Z)-2-(2-amino-5-fluorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (130 mg).

IR (KBr) : 1770, 1612, 1587, 1535, 1392, 1216, 1066 cm^{-1}

NMR (DMSO-d_6, δ) : 2.90 and 3.18 (2H, ABq, J=16.9Hz), 3.45-3.60 (2H, m), 4.10-4.60 (2H, m), 4.99 (1H, d, J=4.8Hz), 5.04 and 5.21 (2H, ABq, J=18.1Hz), 5.61 (1H, dd, J=4.8Hz, 7.9Hz), 5.81 (1H, d, J=3Hz), 6.99 (2H, br s), 7.25 (2H, br s), 8.08 (1H, d, J=3Hz), 9.34 (1H, d, J=7.9Hz), 11.50 (1H, s)

Example 48

A solution of 7β-[(Z)-2-tert-butoxycarbonylmethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (1.43

g) in 4.5 ml of dichloromethane and 1.5 ml of anisole was treated with trifluoroacetic acid (3 ml). After 1 hour, the reaction mixture was poured into isopropyl ether. The precipitates were purified by preparative HPLC to afford 0.15 g of 7β-[(Z)-2-carboxymethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 1772, 1749, 1649, 1541 cm^{-1}

NMR (DMSO-d_6, δ) : 2.88, 3.21 (2H, ABq, J=17.3Hz), 3.59 (2H, br s), 4.3-4.6 (2H, m), 4.48 (2H, br s), 5.06 (1H, d, J=4.9Hz), 5.1-5.3 (2H, m), 5.69 (1H, dd, J=9.2Hz, 4.9Hz), 5.83 (1H, d, J=3.1Hz), 7.33 (2H, br s), 7.42 (2H, br s), 8.07 (1H, d, J=3.1Hz), 10.25 (1H, d, J=9.2Hz)

MS (FAB) m/z : 601.0 (M^+)

Example 49

A solution of 7β-[(Z)-2-(1-tert-butoxycarbonyl-1-methylethoxyimino)-2-(2-amino-5-chlorothiazol-4-yl)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (4.15 g) in 12 ml of dichloromethane and 4 ml of anisole was treated with trifluoroacetic acid (8 ml). After 4 hours, the reaction mixture was poured into isopropyl ether. The precipitates were purified by column chromatography on HP-20 resin and by preparative HPLC to afford 160 mg of 7β-[(Z)-2-(1-carboxy-1-methylethoxyimino)-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 3332, 1774, 1651, 1541 cm^{-1}

NMR (DMSO-d_6, δ) : 1.44 (3H, s), 1.47 (3H, s), 2.95, 3.20 (2H, ABq, J=17.3Hz), 3.59 (2H, br s), 4.38 (2H, br s), 5.05 (1H, d, J=4.9Hz), 5.08, 5.22 (2H, ABq, J=15Hz), 5.66 (1H, dd, J=8.6Hz, 4.9Hz), 5.82 (1H, d, J=3.2Hz), 7.27 (2H, br s), 7.41 (2H, br s), 8.09 (1H, d, J=3.2Hz), 9.61 (1H, d, J=8.6Hz)

MS (FAB) m/z : 629.0 (M^+)

Example 50

Trifluoroacetic acid (0.3 ml) was added to a suspended solution of 7β-[(Z)-2-(2-amino-5-bromothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.15 g) in dichloromethane (0.6 ml) and anisole (0.15 ml) with stirring and ice-cooling. After it was stirred at 5°C for 10 minutes, it was stirred at room temperature for 2 hours. The reaction mixture was poured into diisopropyl ether (30 ml), and the resulting precipitate was collected by filtration. The precipitate was dissolved into water (10 ml) at pH 7.0 with saturated of $NaHCO_3$ solution. After the solution was adjusted to pH 4.0 with 1N-hydrochloric acid, it was subjected to column chromatography on Diaion HP-20 (10 ml). The column was washed with water (50 ml), and the object compound was eluted with 40% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7β-[(Z)-2-(2-amino-5-bromothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.11 g).

IR (KBr) : 1770, 1666, 1645, 1616, 1585, 1539 cm^{-1}

NMR (DMSO-d_6, δ) : 2.89, 3.17 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 4.20-4.60 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.04, 5.21 (2H, ABq, J=16Hz), 5.61 (1H, dd, J=4.9Hz, 8.5Hz), 5.81 (1H, d, J=3.2Hz), 7.26 (2H, s), 7.33 (2H, s), 8.09 (1H, d, J=3.2Hz), 9.31 (1H, d, J=8.5Hz)

MS (FAB) m/z : 587 (M^+), 589 (M^++2)

Example 51

To a suspension of 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (12

g) and anisole (12 ml) in dichloromethane (40 ml) was added dropwise trifluoroacetic acid (36 ml) under ice-cooling with stirring and the mixture was stirred for 3 hours at 5°C to 10°C. The resulting solution was added to isopropyl ether (800 ml). The precipitate was collected by filtration and dried under reduced pressure. The powder was dissolved in water (400 ml), adjusted to pH 4.0 with aqueous sodium hydrogencarbonate and then subjected to column chromatography on HP-20 (300 ml), and eluted with 10% 2-propanol and the eluate was lyophilized to give 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (3.6 g).

IR (KBr) : 1772, 1612, 1538, 1392, 1353, 1064 cm^{-1}

NMR (DMSO-d_6, δ) : 2.90 and 3.28 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 4.20-4.60 (2H, m), 4.98 (1H, d, J=5.0Hz), 5.00 and 5.22 (2H, ABq, J=16Hz), 5.62 (1H, dd, J=5Hz, 8Hz), 5.81 (1H, d, J=3.0Hz), 7.10-7.25 (4H, m), 8.09 (1H, d, J=3.0Hz), 9.32 (1H, d, J=8Hz), 11.70 (1H, br s)

Example 52

A mixture of N,N-dimethylformamide (0.67 ml) and phosphorus oxychloride (0.8 ml) in tetrahydrofuran (23 ml) was stirred for 30 minutes at 5°C. (Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetic acid (2.27 g) was added thereto with stirring and ice-cooling, and the mixture was stirred for 30 minutes at 5°C to produce an activated acid solution. On the other hand, 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (2.7 g) was dissolved in a solution of mono-trimethyl silylacetamide (8 g) in N,N-dimethylformamide (27 ml) and tetrahydrofuran (27 ml). To the solution was at a time added the above obtained activated acid solution at 5°C, and the mixture was stirred for 1.5

hours at 5°C. The resulting solution was poured into ethyl acetate (500 ml). The precipitate was collected by filtration and dried under reduced pressure. The powder was suspended into methanol (30 ml), thereto was added concentrated hydrochloric acid (6.8 ml) at room temperature. After the reaction mixture was stirred at room temperature for 3 hours, the reaction mixture was poured into an ice-cooled water (100 ml) and adjusted to pH 3.5 with aqueous sodium hydrogen carbonate. The resulting solution was evaporated in vacuo by removal of MeOH. To the residual solution was subjected to column chromatography on HP-20 (50 ml), and eluted with 20% 2-propanol and the eluate was lyophilized to give 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (530 mg).

IR (KBr) : 1774, 1618, 1538, 1359, 1220, 1062 cm^{-1}

NMR (DMSO-d_6, δ) : 1.80-2.55 (4H, m), 2.93 and 3.17 (2H, ABq, J=17Hz), 3.40-3.83 (2H, m), 4.20-4.60 (2H, m), 4.98 (1H, d, J=5.0Hz), 5.00-5.30 (3H, m), 5.58 (1H, dd, J=5Hz, 8.5Hz), 5.82 (1H, d, J=3.2Hz), 5.92 (1H, m), 6.07 (1H, m), 7.26 (2H, s), 7.41 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.42 (1H, d, J=8.5Hz)

Example 53

Phosphorus oxychloride (3.52 g) was added to a mixed solution of N,N-dimethylformamide (1.78 ml) and ethyl acetate (5.4 ml) with stirring and ice-cooling. After it was stirred at 5°C for 30 minutes, (Z)-2-(2-formylamino-5-bromothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetic acid (7.5 g) and ethyl acetate (12 ml) was added thereto at the same temperature. After the reaction mixture was stirred at 5°C for 30 minutes, this is referred to as solution (A). On the other hand, N-trimethylsilylacetamide (12.3 g) was added to a suspended mixture of 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate monohydrochloride

(3.87 g) in N,N-dimethylformamide (20 ml) and ethyl acetate (50 ml) at room temperature, and the suspended mixture was warmed at 35°C with stirring for 10 minutes to give a clear solution. The above solution (A) was added to this clear solution with stirring at 5°C, then it was stirred at the same temperature for 2 hours. After that, the reaction mixture was poured into a mixed solution of ethyl acetate (300 ml), diisopropyl ether (50 ml), and methanol (10 ml). The resulting precipitate was collected by filtration, and it was suspended into methanol (60 ml). Concentrated hydrochloric acid (4.5 ml) was added thereto at room temperature. After the reaction mixture was stirred at room temperature for 3 hours, it was poured into water (60 ml), and the solution was adjusted to pH 4.0 with potassium carbonate. It was concentrated to remove methanol, and it was subjected to column chromatography on Diaion HP-20 (100 ml) [Trademark; Mitsubishi Kasei Co.]. The column was washed with water (500 ml), and the object compound was eluted with 40% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7β-[(Z)-2-(2-amino-5-bromothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.22 g).

IR (KBr) : 1772, 1668, 1645, 1616, 1537 cm^{-1}

NMR (DMSO-d_6, δ) : 1.80-2.55 (4H, m), 2.93, 3.17 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 4.20-4.60 (2H, m), 4.99 (1H, d, J=4.9Hz), 5.00-5.30 (3H, m), 5.58 (1H, dd, J=4.9Hz, 8.4Hz), 5.82 (1H, d, J=3.2Hz), 5.92 (1H, m), 6.07 (1H, m), 7.26 (2H, s), 7.41 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.42 (1H, d, J=8.4Hz)

MS (FAB) m/z : 653 (M^+), 655 (M^++2)

Example 54

To an ice-cooling solution of N,N-dimethylformamide (0.20 ml) and ethyl acetate (1.0 ml) was added phosphorus

oxychloride (0.385 g). After it was stirred under ice-cooling for 30 minutes, (Z)-2-(2-formylamino-5-bromothiazol-4-yl)-2-(1-trityl-1H-1,2,3-triazol-5-yl)thiomethoxyimino-acetic acid (1.5 g) was added thereto, and it was stirred at the same temperature for one hour. On the other hand, N-trimethylsilylacetamide (3.03 g) was added to a suspension of 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (0.95 g) in ethyl acetate (5 ml) and N,N-dimethylformamide (10 ml) at room temperature, and it was warmed at 40°C. After it became clear, the reaction mixture was cooled below 5°C, the above solution of acetic acid derivative was added thereto. After it was stirred under ice-cooling for one hour, it was poured into ethyl acetate (40 ml) and diisopropyl ether (300 ml), and the resulting precipitate was collected by filtration. To a suspension of the precipitate in methanol (25 ml) was added concentrated hydrochloric acid (1.13 ml), and it was stirred at room temperature for 3 hours. The reaction mixture was poured into ethyl acetate (20 ml) and diisopropyl ether (80 ml), and the resulting precipitate was collected by filtration. It was dissolved into water (60 ml) at pH 4, subjected to column chromatography on Diaion HP-20 (15 ml). The column was washed with water (150 ml), then the object compound was eluted with 15% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7β-[(Z)-2-(2-amino-5-bromothiazol-4-yl)-2-(1H-1,2,3-triazol-5-yl)thiomethoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.21 g).

NMR (DMSO-d_6, δ) : 2.86, 3.11 (2H, ABq, J=17Hz), 3.60 (2H, s), 4.30-4.50 (2H, m), 4.99 (1H, d, J=4.9Hz), 5.00-5.25 (2H, m), 5.44 (2H, s), 5.54 (1H, dd, J=4.9Hz, 7.9Hz), 5.81 (1H, d, J=3.2Hz), 7.22 (2H, s), 7.45 (2H, s), 8.01 (1H, s), 8.11 (1H, d, J=3.2Hz), 9.39 (1H, d, J=7Hz)

MS (FAB) m/z : 701 (M^++1)

Example 55

To a solution of the mixture of (Z)-2-(1-trityl-1H-tetrazol-5-ylmethoxyimino)-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid and (Z)-2-(2-trityl-2H-tetrazol-5-ylmethoxyimino)-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid (2.14 g) in 22 ml of N,N-dimethylacetamide, powdered potassium carbonate (0.52 g) and methanesulfonyl chloride (0.85 g) were added stepwise at 0°C. On the other hand, a suspension of 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (1.40 g) in 14 ml of N,N-dimethylacetamide was treated portionwise with N-(trimethylsilyl)acetamide (2.94 g) at room temperature. Both reaction mixture were combined at 0°C and stirred for 5.5 hours. The reaction was quenched by dropping into ethyl acetate to get precipitates, and which were dissolved in 10 ml of methanol and treated with concentrated hydrochloric acid. The reaction was quenched by dropping into ethyl acetate to get precipitates, and which were purified by column chromatography on HP-20 resin and preparative liquid chromatography to get 0.06 g of 7β-[(Z)-2-(tetrazol-5-ylmethoxyimino)-2-(5-chloro-2-aminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 3412, 1772, 1635 cm^{-1}

NMR (DMSO-d_6, δ) : 2.86, 3.17 (2H, ABq, J=17.4Hz), 3.59 (2H, m), 4.34 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.15 (2H, m), 5.33 (2H, s), 5.65 (1H, dd, J=8.5Hz, 4.9Hz), 5.83 (1H, d, J=3.2Hz), 7.21 (2H, br s), 7.39 (2H, br s), 8.05 (1H, d, J=3.2Hz), 10.03 (1H, d, J=8.5Hz)

MS (FAB) m/z : 625.0

Example 56

Potassium carbonate (0.71 g) was added to an ice-cooling solution of (Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-(1-methylpyrazol-4-yl)methoxyiminoacetic acid (2.19 g) in N,N-dimethylacetamide (20 ml), and it was stirred at 5-10°C for 20 minutes. After methanesulfonyl chloride (1.17 g) was added dropwise to the solution below 10°C, it was stirred under ice-cooling for one hour. On the other hand, N-trimethylsilylacetamide (7.1 g) was added to a suspension of 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (2.23 g) in ethyl acetate (10 ml) and N,N-dimethylformamide (20 ml) at room temperature, and it was warmed at 40°C. After it became clear, the reaction mixture was cooled below 5°C, the above N,N-dimethylacetamide solution was added thereto. After it was stirred under ice-cooling for one hour, it was poured into ethyl acetate (50 ml) and diisopropyl ether (400 ml), and the resulting precipitate was collected by filtration. To a suspension of the precipitate in methanol (20 ml) was added concentrated hydrochloric acid (2 ml), and it was stirred at room temperature for 2 hours. The reaction mixture was poured into ethyl acetate (20 ml) and diisopropyl ether (80 ml), then the resulting precipitate was collected by filtration. It was dissolved into water (70 ml) at pH 4, and subjected to column chromatography on Diaion HP-20 (20 ml). The column was washed with water (200 ml), then the object compound was eluted with 15% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(1-methylpyrazol-4-yl)methoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.45 g).

NMR (DMSO-d_6, δ) : 2.88, 3.18 (2H, ABq, J=17Hz), 3.50-3.65 (2H, m), 3.78 (3H, s), 4.30-4.60 (2H, m), 4.96 (2H, s), 4.97 (1H, d, J=4.9Hz), 5.03-5.25 (2H, m), 5.59 (1H, dd, J=4.9Hz, 8.4Hz), 5.82 (1H, d,

J=3.2Hz), 7.27 (2H, s), 7.35 (2H, s), 7.42 (1H, s), 7.69 (1H, s), 8.10 (1H, d, J=3.2Hz), 9.47 (1H, d, J=8.4Hz)

MS (FAB) m/z : 637 (M^+)

Example 57

Potassium carbonate (332 mg) was added to an ice-cooling solution of (Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-(1-tert-butoxycarbonylpyrazol-4-yl)methoxyiminoacetic acid (1.72 g) in N,N-dimethylacetamide (17 ml), and it was stirred at 5-10°C for 10 minutes. After methanesulfonyl chloride (0.50 g) was added dropwise to the solution below 10°C, it was stirred under ice-cooling for one hour. On the other hand, N-trimethylsilylacetamide (4.2 g) was added to a solution of 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (1.32 g) in ethyl acetate (8 ml) and N,N-dimethylformamide (16 ml) at room temperature, and it was warmed at 40°C. After it became clear, the reaction mixture was cooled below 5°C, and the above N,N-dimethylacetamide solution was added thereto. After it was stirred under ice-cooling for one hour, it was poured into ethyl acetate (40 ml) and diisopropyl ether (350 ml), and the resulting precipitate was collected by filtration. To a suspension of the precipitate in methanol (20 ml) was added concentrated hydrochloric acid (1.67 ml), and it was stirred at room temperature for 2 hours. The reaction mixture was poured into ethyl acetate (20 ml) and diisopropyl ether (80 ml), then the resulting precipitate was collected by filtration. To a suspension of the precipitate in dichloromethane (2 ml) and anisole (1 ml) was added trifluoroacetic acid (3 ml) under ice-cooling, then it was stirred at room temperature for one hour. The reaction mixture was poured into diisopropyl ether (40 ml), and the resulting precipitate was collected by filtration. It was dissolved into water (80 ml) at pH 4, and subjected to column

chromatography on Diaion HP-20 (25 ml). The column was washed with water (250 ml), then the object compound was eluted with 15% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(pyrazol-4-yl)-methoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.22 g).

NMR (DMSO-d_6, δ) : 2.88, 3.18 (2H, ABq, J=17Hz), 3.50-3.70 (2H, m), 4.20-4.60 (2H, m), 4.90-5.30 (5H, m), 5.59 (1H, dd, J=4.8Hz, J=8.6Hz), 5.82 (1H, d, J=3.2Hz), 7.25 (2H, s), 7.35 (2H, s), 7.63 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.48 (1H, d, J=8.6Hz)

MS (FAB) m/z : 623 (M^+)

Example 58

Phosphorus pentachloride (1.68 g) was suspended into dichloromethane (18 ml), then it was cooled to -20°C, and (Z)-2-(2-amino-5-iodothiazol-4-yl)-2-acetoxyiminoacetic acid (2.6 g) was added thereto. After it was stirred at -15°C for 2 hours, diisopropyl ether (20 ml) was added thereto, and the resulting precipitate was collected by filtration. On the other hand, 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate monohydrochloric acid salt (2.14 g) was suspended into ethyl acetate (15 ml) and N,N-dimethylformamide (25 ml), and then N-trimethylsilyl-acetamide (6.8 g) was added thereto. It was warmed at 35°C with stirring for 10 minutes to give a clear solution. The precipitate which was synthesized above was added to the clear solution with stirring at 5°C, then it was stirred at the same temperature for an hour. After that, the reaction mixture was poured into a mixed solution of ethyl acetate (200 ml), diisopropyl ether (50 ml), and methanol (50 ml). The resulting precipitate was collected by filtration, and it was suspended into methanol (25 ml). Concentrated hydrochloric acid (2.0 ml) was added thereto at room

temperature. After the reaction mixture was stirred at room temperature for 2 hours, it was poured into water (25 ml), and the solution was adjusted to pH 4.0 with potassium carbonate. It was concentrated to remove methanol, and it was subjected to column chromatography on Diaion HP-20 (90 ml) [Trademark; Mitsubishi Kasei Co.]. The column was washed with water (500 ml), and the object compound was eluted with 40% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7β-[(Z)-2-(2-amino-5-iodothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.18 g).

IR (KBr) : 1770, 1645, 1614, 1537 cm^{-1}

NMR (DMSO-d_6, δ) : 2.91, 3.18 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 4.20-4.60 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.05, 5.22 (2H, ABq, J=16Hz), 5.62 (1H, dd, J=4.9Hz, 8.5Hz), 5.82 (1H, d, J=3.1Hz), 7.29 (4H, s), 8.09 (1H, d, J=3.1Hz), 9.25 (1H, d, J=8.5Hz), 11.64 (1H, s)

MS (FAB) m/z : 635 (M^++1)

Example 59

N-Bromosuccinimide (0.68 g) was added to a solution of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (1.0 g) in N,N-dimethylacetamide (10 ml) with ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ethyl acetate (80 ml) and diisopropyl ether (20 ml), and the resulting precipitate was collected by filtration. The precipitate was dissolved into water (40 ml) at pH 6.5, and then the solution was adjusted to pH 4.0 with 1N-hydrochloric acid. It was subjected to column chromatography on Diaion HP-20 (30 ml) [Trademark; Mitsubishi Kasei Co.]. The column was washed with water (200 ml), and the object compound was

eluted with 30% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7β-[(Z)-2-(2-amino-5-bromothiazol-4-yl)-2-methoxyimino-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.25 g).

IR (KBr) : 1770, 1649, 1614, 1537 cm^{-1}

NMR (DMSO-d_6, δ) : 2.92, 3.20 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 3.84 (3H, s), 4.20-4.60 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.06, 5.21 (2H, ABq, J=15Hz), 5.60 (1H, dd, J=4.9Hz, 8.5Hz), 5.82 (1H, d, J=3.2Hz), 7.27 (2H, s), 7.41 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.49 (1H, d, J=8.5Hz)

MS (FAB) m/z : 601 (M^+), 603 (M^++2)

Example 60

7β-[(Z)-2-(2-Amino-5-iodothiazol-4-yl)-2-methoxyimino-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate was obtained according to a similar manner to that of Example 59.

IR (KBr) : 1772, 1649, 1614, 1535, 1039 cm^{-1}

NMR (DMSO-d_6, δ) : 2.92, 3.20 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 3.86 (3H, s), 4.20-4.60 (2H, m), 4.99 (1H, d, J=4.8Hz), 5.06, 5.20 (2H, ABq, J=15Hz), 5.59 (1H, dd, J=4.8Hz, 8.5Hz), 5.82 (1H, d, J=3.2Hz), 7.27 (2H, s), 7.38 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.43 (1H, d, J=8.5Hz)

MS (FAB) m/z : 649 (M^++1)

The following compounds (Examples 61 to 66) were obtained according to a similar manner to that of Example 3.

Example 61

7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-methoxyiminoacetamido] -3-(4,5,6,7-tetrahydro-1-pyrazolo-[1,5-a]pyrimidinio)methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1619, 1538, 1438, 1243, 1037 cm^{-1}

NMR (DMSO-d_6, δ) : 1.85-2.30 (2H, m), 3.1-3.80 (4H, m), 3.84 (3H, s), 4.00-4.25 (2H, m), 4.94 and 5.26 (2H, ABq, J=15Hz), 4.99 (1H, d, J=4.8Hz), 5.58 (1H, dd, J=8.3Hz, 4.8Hz), 5.80 (1H, d, J=3.1Hz), 7.39 (2H, br s), 7.94 (1H, br s), 8.07 (1H, d, J=3.1Hz), 9.48 (1H, d, J=8.3Hz)

Example 62

7β-[(Z)-2-Ethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)-acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]-methyl-3-cephem-4-carboxylate

IR (KBr) : 3390, 1772, 1608, 1539 cm^{-1}

NMR (DMSO-d_6, δ) : 1.24 (3H, t, J=7.0Hz), 3.11, 3.33 (2H, ABq, J=17.2Hz), 4.02 (2H, t, J=8.8Hz), 4.11 (2H, q, J=7.0Hz), 4.26 (1H, q, J=8.8Hz), 4.52 (1H, q, J=8.8Hz), 4.97, 5.08 (2H, ABq, J=14.6Hz), 5.01 (1H, d, J=4.9Hz), 5.59 (1H, dd, J=4.9, 8.5Hz), 5.87 (1H, d, J=3.0Hz), 7.38 (2H, br s), 8.23 (1H, d, J=3.0Hz), 9.44 (1H, d, J=8.5Hz)

MS (FAB) m/z : 553.0 (M^+), 555.0 (M^++2)

Example 63

7β-[(Z)-2-Ethoxyimino-2-(2-amino-5-bromothiazol-4-yl)-acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]-methyl-3-cephem-4-carboxylate

IR (KBr) : 3390, 1770, 1608, 1537 cm^{-1}

NMR (DMSO-d_6, δ) : 1.25 (3H, t, J=7.0Hz), 3.11, 3.32 (2H, ABq, J=17.0Hz), 4.02 (2H, m), 4.11 (2H, q, J=7.0Hz), 4.26 (1H, q, J=8.9Hz), 4.52 (1H, q, J=8.3Hz), 4.9-5.1 (2H, m), 5.01 (1H, d, J=4.9Hz), 5.59 (1H, dd, J=4.9, 8.5Hz), 5.87 (1H, d, J=3.0Hz), 7.42 (2H, br s), 7.8 (1H, br s), 8.23 (1H, d, J=3.0Hz), 9.44 (1H, d, J=8.5Hz)

MS (FAB) m/z : 597.1 (M^+)

Example 64

7β-[(Z)-2-Methoxyimino-2-(2-amino-5-chlorothiazol-4-yl)-acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]-methyl-3-cephem-4-carboxylate

IR (KBr) : 3392, 1770, 1608, 1539 cm^{-1}

NMR (DMSO-d_6, δ) : 3.12, 3.34 (2H, ABq, J=17.3Hz), 3.84 (3H, s), 4.02 (2H, m), 4.26 (1H, q, J=8.7Hz), 4.52 (1H, q, J=8.3Hz), 4.95-5.12 (2H+1H, m), 5.60 (1H, dd, J=4.8, 8.5Hz), 5.87 (1H, d, J=2.9Hz), 7.42 (2H, br s), 8.03 (1H, br s), 8.25 (1H, d, J=2.9Hz), 9.49 (1H, d, J=8.5Hz)

MS (FAB) m/z : 539.1 (M^+)

Example 65

7β-[(Z)-2-Acetoxyimino-2-(2-amino-5-chlorothiazol-4-yl)-acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]-methyl-3-cephem-4-carboxylate

MS (FAB) m/z : 567.1 (M^+), 569.2 (M^++2)

Example 66

7β-[(Z)-2-Cyanomethoxyimino-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]methyl-3-cephem-4-carboxylate

MS (FAB) m/z : 592.1 (M^+)

Example 67

To a solution of 7β-amino-3-(4,5,6,7-tetrahydro-1-pyrazolo[1,5-a]pyrimidinio)methyl-3-cephem-4-carboxylate (1 g) and monotrimethylsilylacetamide (3.37 g) in a mixture of tetrahydrofuran (10 ml) and N,N-dimethylformamide (10 ml) was added (Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-ethoxyiminoacetyl chloride hydrochloride (0.85 g) in one portion at 5°C under stirring. The stirring was continued for 1.5 hours at the same temperature. The reaction mixture was poured into ethyl acetate (300 ml) to form the

precipitates and then the resulting precipitates were collected by filtration and dried in vacuo. The powder was dissolved in a water (50 ml), and adjusted to pH 3.0 with aqueous sodium hydrogencarbonate. Subsequently, the solution was subjected to column chromatography on HP-20 [Trademark; Mitsubishi Kasei Corporation] (30 ml) and eluted with 20% aqueous isopropyl alcohol, and the eluate was lyophilized to give 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-ethoxyimino]-acetamido-3-(4,5,6,7-tetrahydro-1-pyrazolo[1,5-a]-pyrimidinio)methyl-3-cephem-4-carboxylate (249 mg).

IR (KBr) : 1774, 1666, 1619, 1538, 1322, 1037 cm^{-1}

NMR (DMSO-d_6, δ) : 1.23 (3H, t, J=7.1Hz), 1.80-2.25 (2H, m), 3.0-3.4 (4H, m), 4.00-4.30 (4H, m), 4.86 and 5.28 (2H, ABq, J=15Hz), 5.00 (1H, d, J=4.9Hz), 5.61 (1H, dd, J=8.4Hz, 4.9Hz), 5.80 (1H, d, J=3.1Hz), 7.39 (2H, br s), 8.02 (1H, br s), 8.06 (1H, d, J=3.1Hz), 9.48 (1H, d, J=8.4Hz)

Example 68

7β-[(Z)-2-Fluoromethoxyimino-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]methyl-3-cephem-4-carboxylate was obtained according to a similar manner to that of Example 22.

Example 69

To a solution of 7β-amino-3-(4,5,6,7-tetrahydro-1-pyrazolo[1,5-a]pyrimidinio)methyl-3-cephem-4-carboxylate (3 g) and monotrimethylsilylacetamide (10.1 g) in a mixture of tetrahydrofuran (30 ml) and N,N-dimethylformamide (30 ml) was added (Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-acetoxyiminoacetyl chloride (2.86 g) in one portion at 5°C under stirring. The stirring was continued for 1.5 hours at the same temperature. The reaction mixture was poured into ethyl acetate (800 ml) to form the precipitates and then the resulting precipitates were collected by filtration, and

dried in vacuo to give 7β-[(Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-acetoxyimino]acetamido-3-(4,5,6,7-tetrahydro-1-pyrazolo[1,5-a]pyrimidinio)methyl-3-cephem-4-carboxylate (5 g).

NMR (DMSO-d_6, δ) : 2.00-2.25 (2H, m), 2.21 (3H, s), 3.25-3.65 (4H, m), 4.0-4.35 (2H, m), 5.20-5.45 (3H, m), 5.8-6.0 (2H, m), 8.0 (1H, br s), 8.08 (1H, d, J=3.1Hz), 9.98 (1H, d, J=8.3Hz), 13.0 (1H, br s)

The following compounds (Examples 70 to 72) were obtained according to a similar manner to that of Example 7.

Example 70

7β-[(Z)-2-Fluoromethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]-pyrazolio)]methyl-3-cephem-4-carboxylate

IR (KBr) : 3429, 1770, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 3.09, 3.34 (2H, ABq, J=17.1Hz), 4.02 (2H, t, J=8.1Hz), 4.26 (1H, q, J=8.1Hz), 4.54 (1H, q, J=8.1Hz), 4.9-5.1 (2H, m), 5.02 (1H, d, J=4.8Hz), 5.57 (1H, s), 5.60 (1H, dd, J=4.8, 8.3Hz), 5.86 (1H, s), 5.87 (1H, d, J=3.0Hz), 7.46 (2H, br s), 8.24 (1H, d, J=3.0Hz), 9.67 (1H, d, J=8.3Hz)

MS (FAB) m/z : 557.0 (M^+)

Example 71

7β-[(Z)-2-Hydroxyimino-2-(2-amino-5-chlorothiazol-4-yl)-acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]-methyl-3-cephem-4-carboxylate

IR (KBr) : 3390, 1772, 1603 cm^{-1}

NMR (DMSO-d_6, δ) : 3.08, 3.31 (2H, ABq, J=17.2Hz), 4.01 (2H, m), 4.25 (1H, q, J=8.7Hz), 4.53 (1H, q, J=8.0Hz), 5.00 (1H, d, J=4.7Hz), 4.97, 5.08 (2H, ABq, J=14.4Hz), 5.61 (1H, dd, J=4.7, 8.2Hz), 5.87

(1H, d, J=2.9Hz), 7.31 (2H, br s), 8.23 (1H, d, J=2.9Hz), 9.31 (1H, d, J=8.2Hz)

MS (FAB) m/z : 525.2 (M^++1)

Example 72

7β-[(Z)-2-Cyanomethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]-pyrazolio)]methyl-3-cephem-4-carboxylate

IR (KBr) : 3413, 1772, 1606 cm^{-1}

NMR (DMSO-d_6, δ) : 3.09, 3.35 (2H, ABq, J=17.2Hz), 4.02 (2H, t, J=8.6Hz), 4.26 (1H, q, J=8.6Hz), 4.53 (1H, q, J=8.6Hz), 5.0-5.1 (2H+2H+1H, m), 5.59 (1H, dd, J=4.8Hz, 8.4Hz), 5.87 (1H, d, J=3.0Hz), 7.47 (2H, br s), 7.84 (1H, br s), 8.24 (1H, d, J=3.0Hz), 9.68 (1H, d, J=8.4Hz)

MS (FAB) m/z : 564.0 (M^+), 566.0 (M^++2)

Example 73

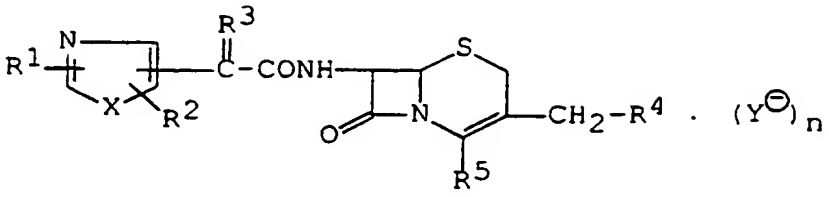
7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido] -3-(4,5,6,7-tetrahydro-1-pyrazolo-[1,5-a]pyrimidinio)methyl-3-cephem-4-carboxylate was obtained according to a similar manner to that of Example 5.

IR (KBr) : 1772, 1619, 1538, 1520, 1245, 1178 cm^{-1}

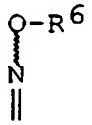
NMR (DMSO-d_6, δ) : 1.8-2.20 (2H, m), 2.95-3.80 (4H, m), 4.0-4.25 (2H, m), 4.96 and 5.28 (2H, ABq, J=15Hz), 4.99 (1H, d, J=5Hz, 8.4Hz), 5.80 (1H, d, J=3.1Hz), 7.31 (2H, br s), 8.03 (1H, br s), 8.06 (1H, d, J=3.1Hz), 9.31 (1H, d, J=8.41Hz), 11.78 (1H, br s)

C L A I M S

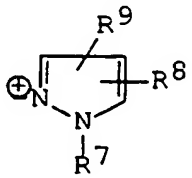
1. A cephem compound of the formula :



wherein R^1 is amino or a protected amino,
R^2 is halogen, lower alkyl, cyano or lower alkylthio,
R^3 is a group of the formula :



[wherein
R^6 is hydrogen, lower alkyl which may have one or more substituent(s), lower alkenyl which may have one or more substituent(s), lower alkynyl, cyclo(lower)alkenyl, or acyl],
lower alkylidene or oxo,
R^4 is a group of the formula :

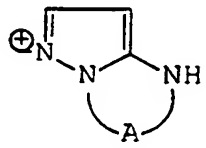


[wherein
R^7 is hydroxy(lower)alkyl or protected hydroxy(lower)alkyl,

R^8 is amino or a protected amino, and

R^9 is hydrogen or lower alkyl],

or a group of the formula :



(wherein A is lower alkylene),

R^5 is $-COO^{\ominus}$, carboxy or a protected carboxy,

X is -S- or -O-,

$Y^{\ominus}$ is an anion, and

n is 0 or 1,

with proviso that

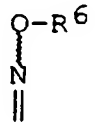
(i) when R^5 is $-COO^{\ominus}$, then n is 0, and

(ii) when R^5 is carboxy or a protected carboxy, then n is 1,

and a salt thereof.

2. A compound of claim 1, wherein

R^3 is a group of the formula :

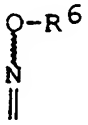


[wherein R^6 is hydrogen;

lower alkyl which may have 1 to 3 substituent(s) selected from the group consisting of halogen, cyano, aryl, lower alkylthio, carboxy, protected carboxy, hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, heterocyclic group which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl and ar(lower)alkyl, and

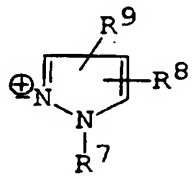
heterocyclicthio;
lower alkenyl which may have 1 to 3 substituent(s) selected from the group consisting of carboxy and protected carboxy;
lower alkynyl;
cyclo(lower)alkenyl; or acyl],
lower alkylidene or oxo.

3. A compound of claim 2, wherein
R^1 is amino, lower alkanoylamino, lower alkoxycarbonylamino or triphenyl(lower)alkylamino,
R^3 is a group of the formula :

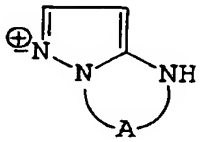


[wherein R^6 is hydrogen; lower alkyl; halo(lower)alkyl; dihalo(lower)alkyl; cyano(lower)alkyl; triphenyl(lower)alkyl; lower alkylthio(lower)alkyl; carboxy(lower)alkyl; lower alkoxycarbonyl(lower)alkyl; carbamoyl(lower)alkyl; hydroxy(lower)alkyl; lower alkanoyloxy(lower)alkyl; heterocyclic(lower)alkyl, in which heterocyclic moiety is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), which may have lower alkyl or triphenyl(lower)alkyl; heterocyclicthio(lower)alkyl, in which heterocyclic moiety is unsaturated 3 to 8-membered

heteromonocyclic group containing 1 to 4 nitrogen atom(s);
lower alkenyl; carboxy(lower)alkenyl; lower alkoxycarbonyl(lower)alkenyl; lower alkynyl; cyclo(lower)alkenyl; or lower alkanoyl],
lower alkylidene, or oxo,
R^4 is a group of the formula :

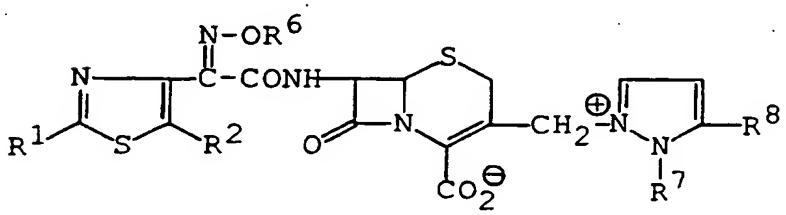


[wherein R^7 is hydroxy(lower)alkyl, lower alkanoyloxy(lower)alkyl, carbamoyloxy(lower)alkyl,
R^8 is amino or lower alkanoylamino, and
R^9 is hydrogen],
or a group of the formula :



(wherein A is lower alkylene).

4. A compound of claim 3, which is a compound of the formula :



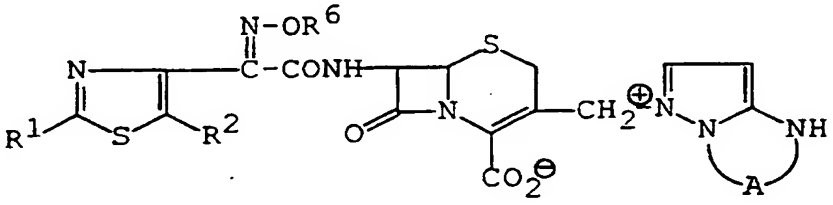
wherein R^1 is amino,
R^2 is as defined above,
R^6 is as defined above,
R^7 is hydroxy(lower)alkyl, and
R^8 is amino.

5. A compound of claim 4, wherein
R^2 is halogen, and
R^6 is halo(lower)alkyl or cyano(lower)alkyl.

6. A compound of claim 5, which is
7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(2-fluoroethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

7. A compound of claim 5, which is
7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-cyanomethoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

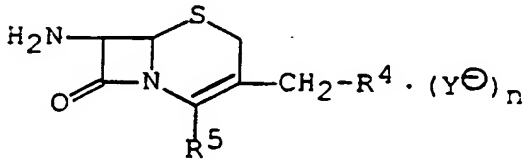
8. A compound of claim 3, which is a compound of the formula :



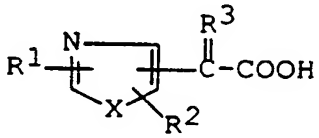
wherein R^1 is amino,
R^2 is halogen,
R^6 is hydrogen, lower alkyl,
halo(lower)alkyl, cyano(lower)alkyl, or
lower alkanoyl, and
A is lower alkylene.

9. A process for the preparation of a cephem compound of claim 1 or a salt thereof, which comprises

1) reacting a compound of the formula :

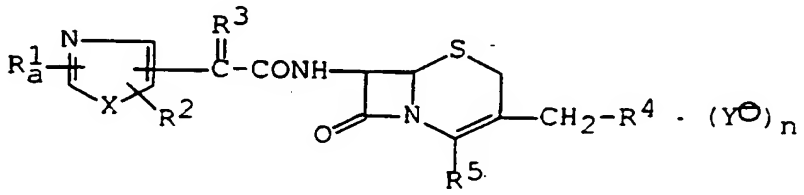


or its reactive derivative at the amino group, or a salt thereof, with a compound of the formula :

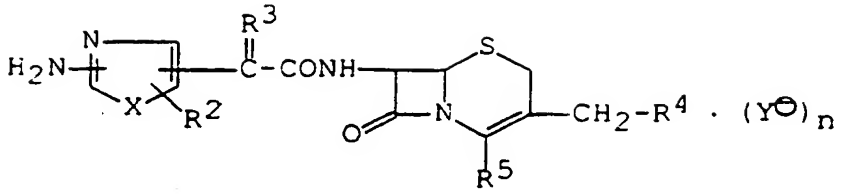


or its reactive derivative at the carboxy group, or a salt thereof, or

2) subjecting a compound of the formula :

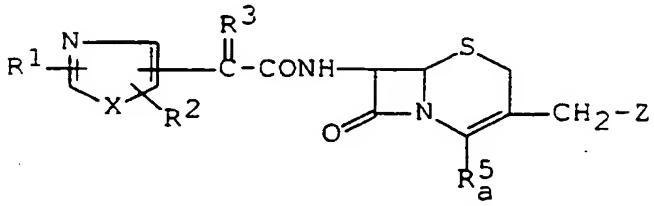


or a salt thereof, to elimination reaction of the amino protective group in R_a^1, to give a compound of the formula :



or a salt thereof, or

3) reacting a compound of the formula :

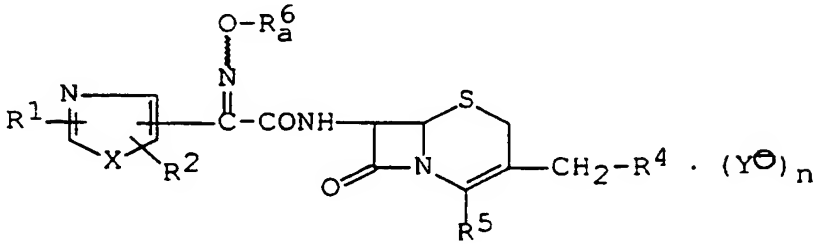


or a salt thereof, with a compound of the formula :

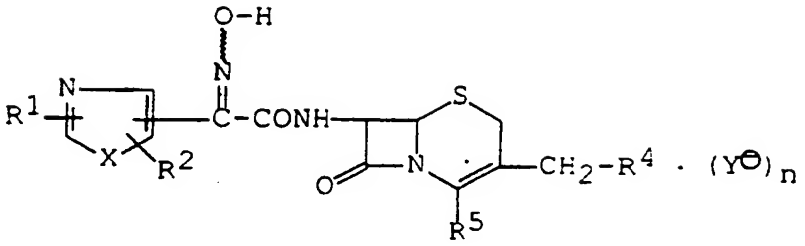
R^4_a

or a salt thereof, or

4) subjecting a compound of the formula :

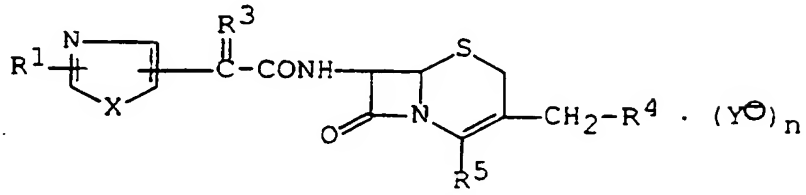


or a salt thereof, to elimination of hydroxy protective group, to give a compound of the formula :

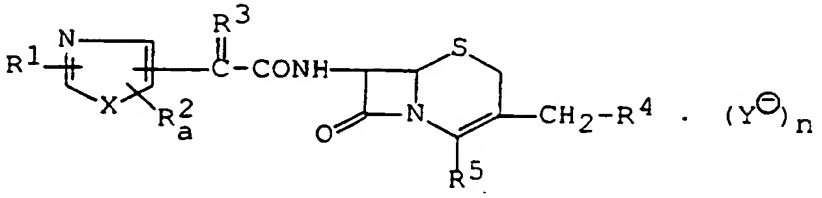


or a salt thereof, or

5) subjecting a compound of the formula :



or a salt thereof, to introduction reaction of halogen, to give a compound of the formula :



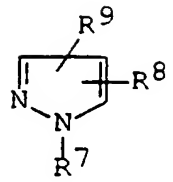
or a salt thereof,

wherein R^1, R^2, R^3, R^4, R^5, X, $Y^{\ominus}$ and n are each as defined in claim 1,

R^1_a is a protected amino,

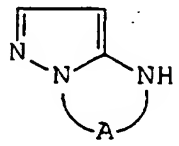
R^2_a is halogen,

R^4_a is a compound of the formula :



(wherein R^7, R^8 and R^9 are each as defined above)

or a compound of the formula :



(wherein A is as defined above),

R^5_a is carboxy or a protected carboxy,

R^6_a is cyclo(lower)alkenyl or acyl,

Z is a leaving group.

10. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

11. A method for the treatment of infectious diseases which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

12. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an antimicrobial agent.

13. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for the preparation of a medicament.

INTERNATIONAL SEARCH REPORT

International Appl. ..on No
PCT/JP 97/01416

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D501/46 A61K31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIE .DS SEARCHED

Minimu n documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 427 248 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 15 May 1991 see claims 1-11	1-13
X	EP 0 332 156 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 13 September 1989 see claims 1-14	1-13
Y	EP 0 149 487 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 24 July 1985 see claims 1-9	1-13
Y	EP 0 287 116 A (EISAI CO., LTD.) 19 October 1988 see claims 1-7; examples 9,10	1-13
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 September 1997	02. 10. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	**Authorized officer** Herz, C

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INTERNATIONAL SEARCH REPORT

International Appl .on No
PCT/JP 97/01416

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 92 00981 A (DAE WOONG PHARMACEUTICAL CO., LTD.) 23 January 1992 see claims 1-17	1-13
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